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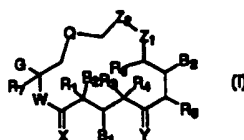
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(54) Title: EPOTHILONE DERIVATIVES



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EPOTHILONE DERIVATIVES

Field of the Invention

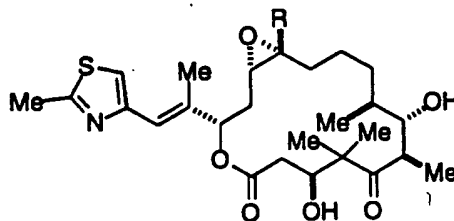
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The present invention relates to epothilone derivatives, methods for the preparation of the derivatives and intermediates therefor.

Background of the Invention

10

Epothilones are macrolide compounds which find utility in the pharmaceutical field. For example, Epothilones A and B having the structures:



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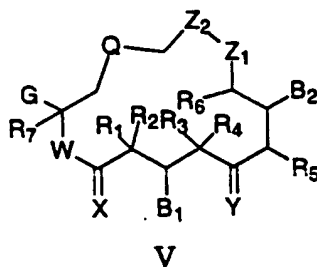
- I Epothilone A R = H
II Epothilone B R = Me

have been found to exert microtubule-stabilizing effects similar to TAXOL and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease, see Angew. Chem. Int. Ed. Engl., 1996, 35, No. 13/14.

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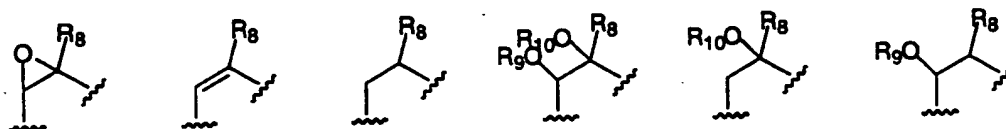
Summary of the Invention

The present invention relates to compounds of the formula



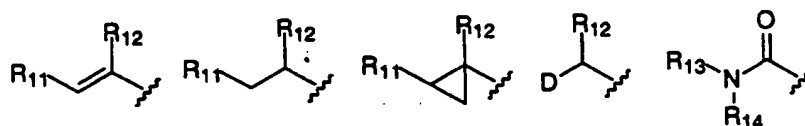
Q is selected from the group consisting of

10



G is selected from the group consisting of alkyl, substituted alkyl, substituted or unsubstituted aryl, heterocyclo,

15



W is O or NR₁₅;

X is O or H, H;

Y is selected from the group consisting of O; H, OR₁₆; OR₁₇, OR₁₇;

20 NOR₁₈; H, NOR₁₉; H, NR₂₀R₂₁; H, H; or CHR₂₂; OR₁₇ OR₁₇ can be a cyclic ketal;

Z₁, and Z₂ are selected from the group consisting of CH₂, O, NR₂₃, S, or SO₂, wherein only one of Z₁ and Z₂ can be a heteroatom;

B₁ and B₂ are selected from the group consisting of OR₂₄, or OCOR₂₅, or O₂CNR₂₆R₂₇; when B₁ is H and Y is OH, H they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of NR₂₈R₂₉, NR₃₀COR₃₁
5 or saturated heterocycle;

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₁₃, R₁₄, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₆, and R₂₇ are selected from the group H, alkyl, substituted alkyl, or aryl and when R₁ and R₂ are alkyl can be joined to form a cycloalkyl; R₃ and R₄ are alkyl can be joined to form a cycloalkyl;

10 R₉, R₁₀, R₁₆, R₁₇, R₂₄, R₂₅, and R₃₁ are selected from the group H, alkyl, or substituted alkyl;

R₈, R₁₁, R₁₂, R₂₈, R₃₀, R₃₂, R₃₃, and R₃₀ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, or heterocycle;

15 R₁₅, R₂₃ and R₂₉ are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocycle, R₃₂C=O, R₃₃SO₂, hydroxy, O-alkyl or O-substituted alkyl; and any salts, solvates or hydrates thereof.

20 Proviso

The present invention does not include compounds of formula V wherein

W and X are both O; and

R₁, R₂, R₇, are H; and

25 R₃, R₄, R₆, are methyl; and

R₈, is H or methyl; and

Z₁, and Z₂, are CH₂; and

G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl;

Q is as defined above.

Detailed Description of the Invention

5

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

10 The term "alkyl" refers to straight or branched chain unsubstituted hydrocarbon groups of 1 to 20 carbon atoms, preferably 1 to 7 carbon atoms. The expression "lower alkyl" refers to unsubstituted alkyl groups of 1 to 4 carbon atoms.

 The term "substituted alkyl" refers to an alkyl group substituted
15 by, for example, one to four substituents, such as, halo, trifluoromethyl, trifluoromethoxy, hydroxy, alkoxy, cycloalkoxy, heterocycloxy, oxo, alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, cycloalkylamino, heterocycloamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or
20 aralkyl, alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido (e.g. SO_2NH_2), substituted sulfonamido,
25 nitro, cyano, carboxy, carbamyl (e.g. CONH_2), substituted carbamyl (e.g. CONH alkyl, CONH aryl, CONH aralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl), alkoxycarbonyl, aryl, substituted aryl, guanidino and heterocyclos, such as, indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl,
30 pyrimidyl and the like. Where noted above where the substituent is further substituted it will be with halogen, alkyl, alkoxy, aryl or aralkyl.

The term "halogen" or "halo" refers to fluorine, chlorine, bromine and iodine.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion,
5 such as phenyl, naphthyl, biphenyl and diphenyl groups, each of which may be substituted.

The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl.

The term "substituted aryl" refers to an aryl group substituted by,
10 for example, one to four substituents such as alkyl; substituted alkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, alkoxy, cycloalkyloxy, heterocycloxy, alkanoyl, alkanoyloxy, amino, alkylamino, aralkylamino, cycloalkylamino, heterocycloamino, dialkylamino, alkanoylamino, thiol, alkylthio, cycloalkylthio, heterocyclothio, ureido,
15 nitro, cyano, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, alkylthiono, arylthiono, alkylsulfonyl, sulfonamido, aryloxy and the like. The substituent may be further substituted by halo, hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

The term "cycloalkyl" refers to optionally substituted, saturated
20 cyclic hydrocarbon ring systems, preferably containing 1 to 3 rings and 3 to 7 carbons per ring which may be further fused with an unsaturated C3-C7 carbocyclic ring. Exemplary groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl, cyclododecyl, and adamantyl. Exemplary substituents include one or
25 more alkyl groups as described above, or one or more groups described above as alkyl substituents.

The terms "heterocycle", "heterocyclic" and "heterocyclo" refer to an optionally substituted, fully saturated or unsaturated, aromatic or nonaromatic cyclic group, for example, which is a 4 to 7 membered
30 monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring system, which has at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a

heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized and the nitrogen heteroatoms may also optionally be quaternized. The heterocyclic group
5 may be attached at any heteroatom or carbon atom.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl,
10 isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl,
15 thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1, 1-dioxothienyl, dioxanyl, isothiazolidinyl, thietanyl, thiiranyl, triazinyl, and triazolyl, and the like.

Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl,
20 benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl) or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzisothiazolyl, benzisoxazolyl, benzodiazinyl,
25 benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl,
30 purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl, and the like.

Exemplary substituents include one or more alkyl groups as described above or one or more groups described above as alkyl

substituents. Also included are smaller heterocycles, such as, epoxides and aziridines.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

5 The compounds of formula V may form salts with alkali metals such as sodium, potassium and lithium, with alkaline earth metals such as calcium and magnesium, with organic bases such as dicyclohexylamine, tributylamine, pyridine and amino acids such as arginine, lysine and the like. Such salts can be obtained, for example, by
10 exchanging the carboxylic acid protons, if they contain a carboxylic acid, in compounds of formula V with the desired ion in a medium in which the salt precipitates or in an aqueous medium followed by evaporation. Other salts can be formed as known to those skilled in the art.

 The compounds for formula V form salts with a variety of organic
15 and inorganic acids. Such salts include those formed with hydrogen chloride, hydrogen bromide, methanesulfonic acid, hydroxyethanesulfonic acid, sulfuric acid, acetic acid, trifluoroacetic acid, maleic acid, benzenesulfonic acid, toluenesulfonic acid and various others (e.g., nitrates, phosphates, borates, tartrates, citrates,
20 succinates, benzoates, ascorbates, salicylates and the like). Such salts are formed by reacting a compound of formula V in an equivalent amount of the acid in a medium in which the salt precipitates or in an aqueous medium followed by evaporation.

 In addition, zwitterions ("inner salts") are formed.

25 Compounds of the formula V may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound for formula V) is a prodrug within the scope and spirit of the invention.

 For example compounds of the formula V may form a carboxylate
30 ester moiety. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid functionalities found on the disclosed ring structure(s).

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Phar Bull, 32, 692 (1984).

It should further be understood that solvates (e.g., hydrates) of the compounds of formula V are also within the scope of the present invention. Methods of solvation are generally known in the art.

Use and Utility

The compounds of formula V are microtubule-stabilizing agents. They are thus useful in the treatment of a variety of cancers or other abnormal proliferative diseases, including (but not limited to) the following;

- carcinoma, including that of the bladder, breast, colon, kidney, liver, lung, ovary, pancreas, stomach, cervix, thyroid and skin; including squamous cell carcinoma;
- hematopoietic tumors of lymphoid lineage, including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma and Burketts lymphoma;
- hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias and promyelocytic leukemia;

- tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;
- other tumors, including melanoma, seminoma, tetratocarcinoma, neuroblastoma and glioma;
- 5 - tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma, and schwannomas;
- tumors of mesenchymal origin, including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and
- other tumors, including melanoma, xenoderma pigmentosum,
- 10 keratoactanthoma, seminoma, thyroid follicular cancer and teratocarcinoma.

Compounds of formula V may also inhibit tumor angiogenesis, thereby affecting abnormal cellular proliferation. Such anti-angiogenesis properties of the compounds of formula V may also be
15 useful in the treatment of certain forms of blindness related to retinal vascularization, arthritis, especially inflammatory arthritis, multiple sclerosis, restinosis and psoriasis.

Compounds of formula V may induce or inhibit apoptosis, a physiological cell death process critical for normal development and
20 homeostasis. Alterations of apoptotic pathways contribute to the pathogenesis of a variety of human diseases. Compounds of formula V, as modulators of apoptosis, will be useful in the treatment of a variety of human diseases with aberrations in apoptosis including cancer (particularly, but not limited to follicular lymphomas, carcinomas with
25 p53 mutations, hormone dependent tumors of the breast, prostate and ovary, and precancerous lesions such as familial adenomatous polyposis), viral infections (including but not limited to herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), autoimmune diseases (including but not limited to systemic lupus
30 erythematosus, immune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel diseases and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's

disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cer bellar degeneration), AIDS, myelodysplastic syndromes, aplastic anemia, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol induced liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis), aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases, and cancer pain.

10 The compounds of this invention are also useful in combination with known anti-cancer and cytotoxic agents and treatments, including radiation. If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within its
15 approved dosage range. Compounds of formula V can be used sequentially with known anticancer or cytotoxic agents and treatment, including radiation when a combination formulation is inappropriate. Especially useful are cytotoxic drug combinations wherein the second drug chosen acts in a different phase of the cell cycle, e.g. S phase, than
20 the present compounds of formula V which exert their effects at the G₂-M phase.

e.g. Thymidilate Synthase Inhibitors,
DNA Cross Linking Agents
25 Topoisomerase I and II Inhibitors
DNA Alkylating Agents
Ribonucleoside Reductase Inhibitors
Cytotoxic Factors e.g. TNF-alpha or
Growth factor inhibitors e.g. HER 2 receptor MAB's

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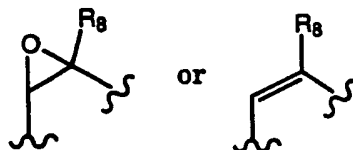
The present compounds may exist as multiple optical, geometric, and stereoisomers. Included within the present invention are all such isomers and mixtures thereof.

The compounds of this invention can be formulated with a pharmaceutical vehicle or diluent for oral, intravenous or subcutaneous administration. The pharmaceutical composition can be formulated in a classical manner using solid or liquid vehicles, diluents and additives appropriate to the desired mode of administration. Orally, the compounds can be administered in the form of tablets, capsules, granules, powders and the like. The compounds are administered in a dosage range of about 0.05 to 200 mg/kg/day, preferably less than 100 mg/kg/day, in a single dose or in 2 to 4 divided doses.

Preferred Compounds

15

Especially preferred compounds of formula V are those wherein



20 X is O

Y is O

Z₁ and Z₂ are CH₂ and

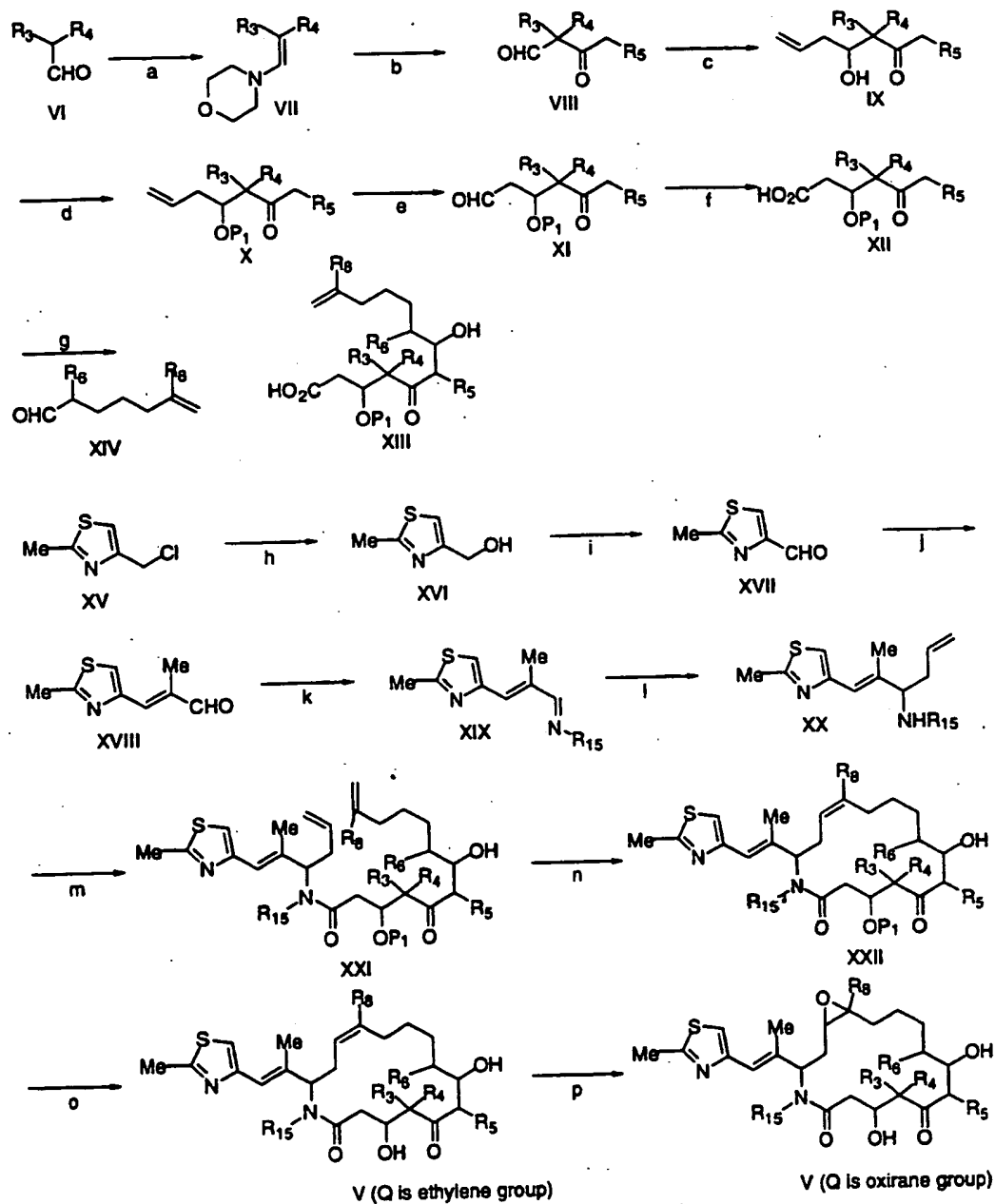
W is NR₁₅.

Method of Preparation

Compounds of formula V are prepared by the following schemes.

Scheme 1

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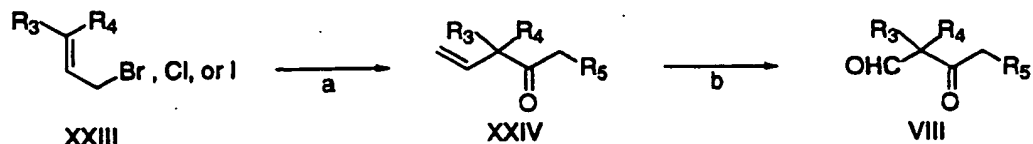


wherein R₃, R₄, R₅, R₆, R₈ and R₁₅ are as above and P₁ is an oxygen protecting group.

Compounds of formula V where W is NR₁₅ and X is O can be prepared as outlined in Scheme 1. A compound of formula XII, where P₁ is an oxygen protecting group such as t-butyldimethylsilyl, can be prepared from a compound of formula VI by known methods (i.e., Nicolaou, K.C., et al., Angew. Chem. Int. Ed. Engl., (1997) 36, 166-168). Aldol reaction of a compound of formula XII and a compound of formula XIV provides a compound of formula XIII. The compound of formula XIV can be prepared by known methods (i.e., Schinzer, D., et al., Eur. Chem. Chron., (1996) 1, 7-10). An aldehyde of formula XVIII can be prepared from a compound of formula XV as shown in Scheme 1 or by using known methods (i.e., Taylor, R.E., et al., Tetrahedron Lett., (1997), 38, 2061-2064). A compound of formula XIX can be prepared from a compound XVIII by treatment with an amine using dehydrating conditions such as catalytic p-toluenesulfonic acid and azeotropic removal of water. A compound of formula XX can be prepared from a compound of formula XIX by treatment with an allylating reagent such as allylmagnesium bromide. A compound of formula XXI can be prepared from compounds of formulas XIII and XX, by standard amide bond coupling agents (i.e., DCC, BOP, EDC/HOBT, PyBrOP). A compound of formula XXII can be prepared from a compound of formula XXI by ring-closing metathesis using either the Grubbs (RuCl₂ (= CHPh)(PCY₃)₂; see Grubbs, R.H., et al., Angew. Chem. Int. Ed. Engl.; (1995) 34, 2039) or Schrock catalysts (See Schrock, R.R., et al., J. Am. Chem. Soc., (1990) 112, 3875). Deprotection of a compound of formula XXI using, for example when P₁ is a t-butyldimethylsilyl group, hydrogen fluoride in acetonitrile or tetra-n-butyl ammonium fluoride in THF provides a compound of formula V where Q is an ethylene group, W is NR₁₅, X is O, and R₃, R₄, R₅, R₆ are defined as described above. Regioselective epoxidation of a compound of formula V where Q is an

ethylene group using dimethyldioxirane provides a compound of formula V where Q is an oxirane group, W is NR_{15} , X is O, and R_3 , R_4 , R_5 , R_{15} are defined as described above.

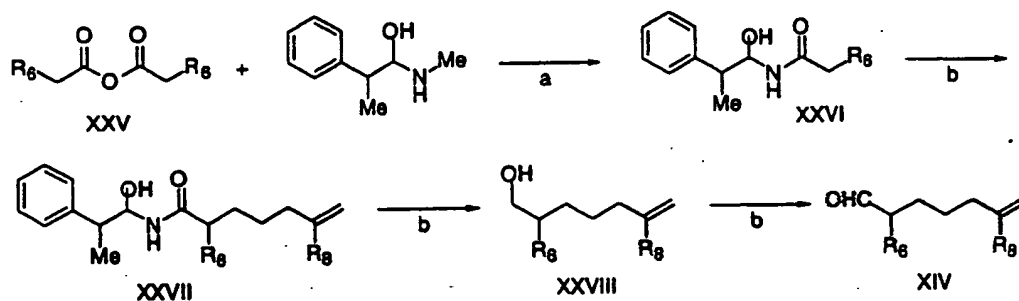
5 Scheme 2



Alternatively, a compound of formula VIII can be prepared by reaction of a compound of formula XXIII with magnesium and an acid chloride ($\text{R}_5\text{CH}_2\text{COCl}$) to give a compound of formula XXIV (See for example: Heathcock, C.; et. al., *J. Org. Chem.*, 1990, 55, 1114-1117), followed by ozonolysis to give a compound of formula VIII as shown in Scheme 2.

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Scheme 3

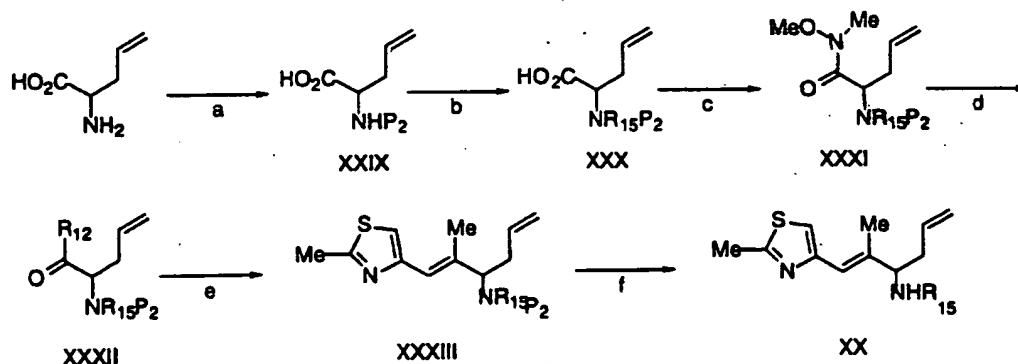


Alternatively, a compound of formula XIV can be prepared as shown in Scheme 3. Reaction of a compound of formula XXV and pseudoephedrine provides a compound of formula XXVI. A compound of formula XXVII can be prepared from a compound of formula XXVI by alkylation with a pentenyl halide such as 5-bromopentene according to the method of Meyers (i.e., Meyers, A.; et. al., *J. Am. Chem. Soc.*,

25

1994, 116, 9361-9362). A compound of formula XXVIII can be prepared from a compound of formula XXVII with a reducing agent such as lithium pyrrolidinyl borohydride. Oxidation of a compound of formula XXVIII, using for example pyridinium chlorochromate, provides a compound of formula XIV. Direct conversion of a compound of formula XXVII to a compound of formula XIV can be accomplished with a reducing agent such as lithium triethoxy-aluminum hydride.

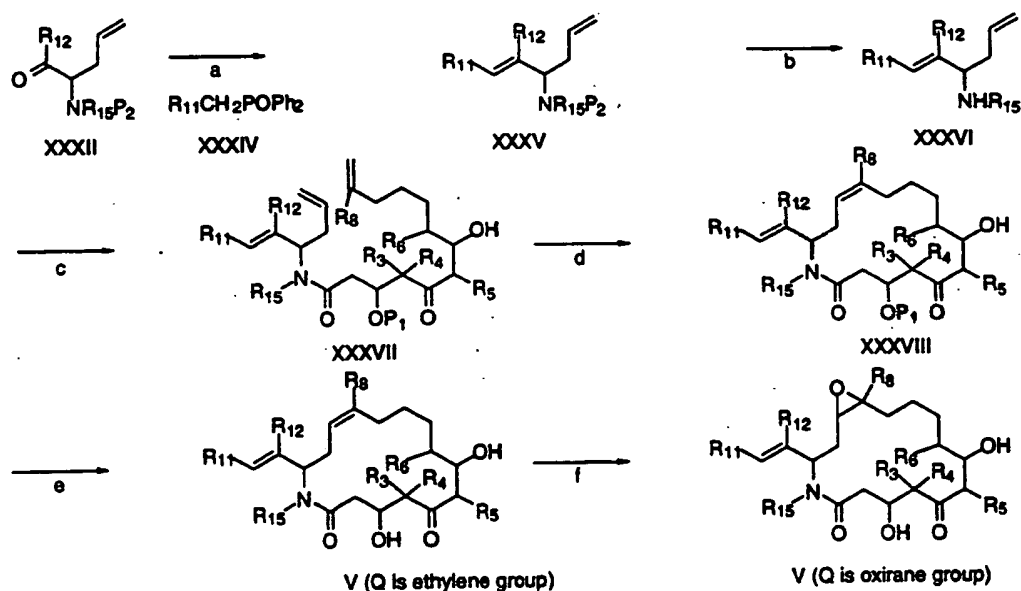
Scheme 4



Alternatively, a compound of formula XX can be prepared from allylglycine as shown in Scheme 4. Allylglycine can be N-protected using methods known in the art to give a compound of formula XXIX, where P₂ is a suitable N-protecting group such as t-butyloxycarbonyl. Optionally, where R₂₉ is not hydrogen, a compound of formula XXX can be prepared from a compound of formula XXIX by alkylation with an alkyl halide in the presence of a base such as sodium hydride. A compound of formula XXXI can be prepared from a compound of formula XXX using N,O-dimethylhydroxylamine and standard coupling agents such as EDCI and HOBt. A compound of formula XXXII can be prepared from a hydroxamate XXXI by treatment with an organometallic reagent such as an alkyl or arylmagnesium halide. Wittig olefination of a compound of formula XXXII provides a compound of formula XXXIII (the Wittig reagent is prepared as reported:

Danishefsky, S.E.; et. al., *J. Org. Chem.*, 1996, 61, 7998-7999). N-D protection of a compound of formula XXXIII using methods known in the art provides a compound of formula XX.

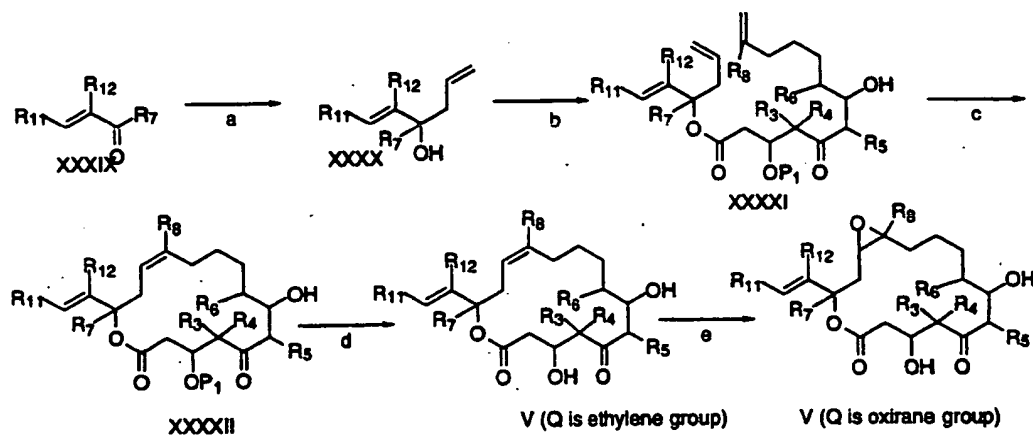
5 **Scheme 5**



- 10 A compound of formula V where W is NR_{15} , X is oxygen, and G is a 1,2-disubstituted olefin can be prepared as shown in Scheme 5. A compound of formula XXXV can be prepared by Wittig olefination of a compound of formula XXXII. A compound of formula XXXIV can be prepared by methods known in the art. A compound of formula XXXVI can be prepared by N-deprotection of a compound of formula XXXV using methods known in the art. A compound of formula XXXVII can be prepared by coupling reaction of a compound of formula XXXVI and a compound of formula XIII using standard coupling agents such as EDCI and HOBT. A compound of formula XXXVIII can be prepared from a compound of formula XXXVII by methods described in Scheme 1 for the preparation of a compound of formula XXII. Using methods
- 15
- 20

described in Scheme 1 (steps o and p), a compound of formula XXXVIII can be converted to compounds of formula V where W is NR₁₅, X is oxygen, and G is a 1,2-disubstituted olefin.

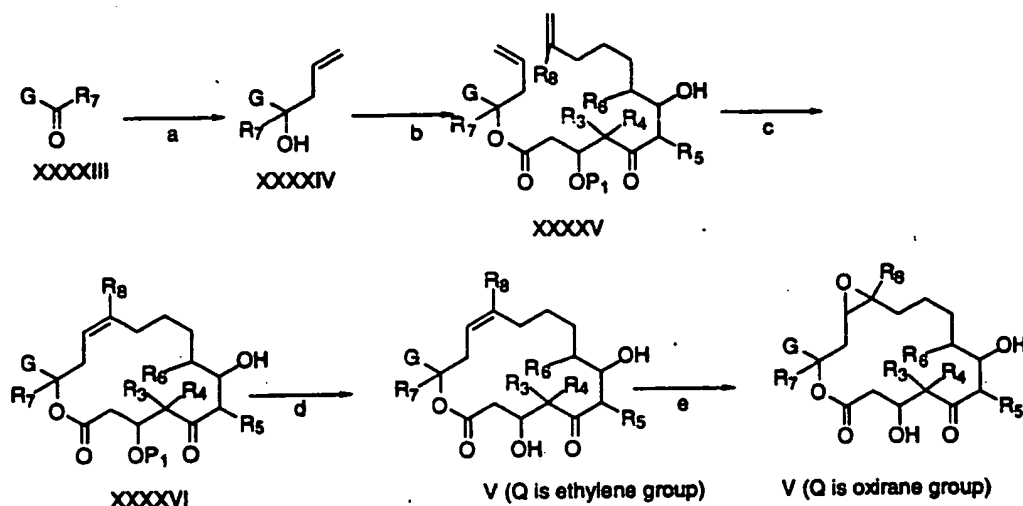
5 Scheme 6



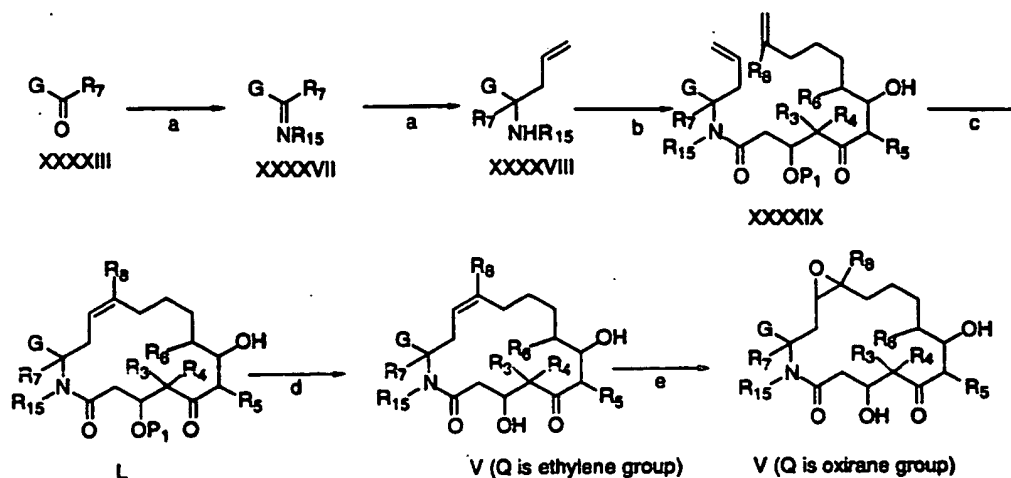
- 10 A compound of formula V where both W and X are oxygen, and G is a 1,2-disubstituted olefin can be prepared as shown in Scheme 6. A compound of formula XXXX can be prepared from a compound of formula XXXIX by treatment with an allylating agent such as allylmagnesium bromide. Enantiomerically pure XXXX can be prepared by employing chiral reagents (see, for example: Taylor, R.E.; et. al., Tetrahedron Lett., 1997, 38, 2061-2064; Nicolaou, K.C.; et. al., Angew. Chem. Int. Ed. Engl., 1997, 36, 166-168, Keck, G., et. al., J. Am. Chem. Soc., 1993, 115, 8467). A compound of formula XXXXI can be prepared from compounds of formula XXXX and XIII by using standard esterification methods such as DCC and DMAP. A compound of formula XXXXII can be prepared from a compound of formula XXXXI via ring-closing olefin metathesis as described in Scheme 1 for the preparation of a compound of formula XXII. Compounds of formula V where both W and X are oxygen, and G is a 1,2-disubstituted
- 15
- 20

olefin can be prepared from a compound of formula XXXXII by deprotection (where Q is an ethylene group) and, if desired, epoxidation (where Q is an oxirane group) as described above.

5 Scheme 7



A compound of formula V where both W and X are oxygen, and G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl can be prepared as shown in Scheme 7. A compound of formula XXXXIV can be prepared by allylation of a compound of formula XXXXIII, where G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl, by reaction with an allylating reagent such as allyl magnesium bromide. A compound of formula XXXXV can be prepared from a compound of formula XXXXIV via esterification with a compound of formula XIII using, for example, DCC and DMAP. A compound of formula XXXXVI can be prepared from a compound of formula XXXXV by ring-closing metathesis as described above. Following the methods outlined above for Scheme 1, a compound of formula XXXXVI can be converted to compounds of formula V by deprotection and subsequent epoxidation.

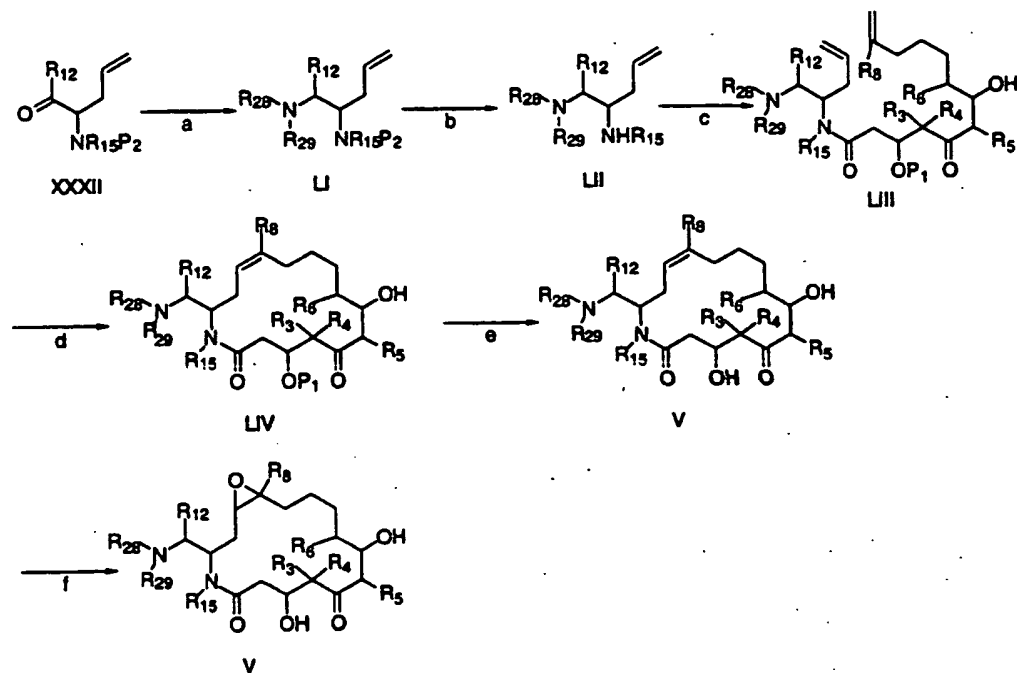
Scheme 8

A compound of formula V where W is NR₁₅, X is oxygen, and G is

5 alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl can be prepared as shown in Scheme 8. A compound of formula XXXXVII can be prepared by reaction of a compound of formula XXXXIII, where G is alkyl, substituted alkyl, aryl, heteroaryl, bicycloaryl, or bicycloheteroaryl, and an amine under dehydrating

10 conditions. A compound of formula XXXXVIII can be prepared from a compound of formula XXXXVII by treatment with an allylating agent such as allylmagnesium bromide. A compound of formula XXXXIX can be prepared from a compound of formula XXXXVIII and a compound of formula XIII by standard amide bond coupling techniques using, for example, EDCI and HOBT. A compound of formula L can be

15 prepared from a compound of formula XXXXIX by ring-closing metathesis as described above. Following the methods outlined above for Scheme 1, a compound of formula L can be converted to compounds of formulas V by deprotection and subsequent epoxidation.

Scheme 9

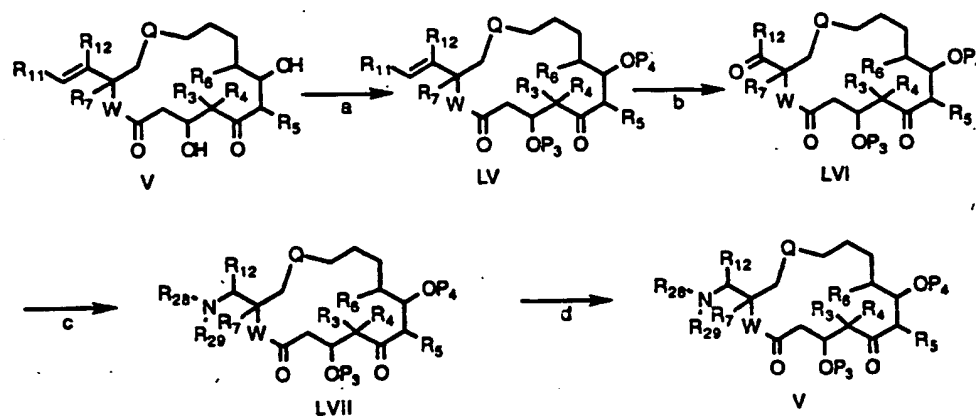
A compound of formula V where X is oxygen, W is NR₁₅, and G is



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and D is selected from the group consisting of NR₂₈R₂₉, NR₃₀COR₃₁, and saturated heterocycle (i.e., piperidinyl, morpholinyl, piperazinyl, etc.) can be prepared as shown in Scheme 9. A compound of formula LI can be prepared from a compound of formula XXXII by reductive amination using a primary or secondary amine and a reducing agent such as sodium triacetoxyborohydride. Compounds of formula LIII, LIV, and V can then be prepared following methods described above in Scheme 1.

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Scheme 10

- 5 Alternatively, a compound of formula V where X is oxygen, W is oxygen or NR₁₅ or oxygen, and G is

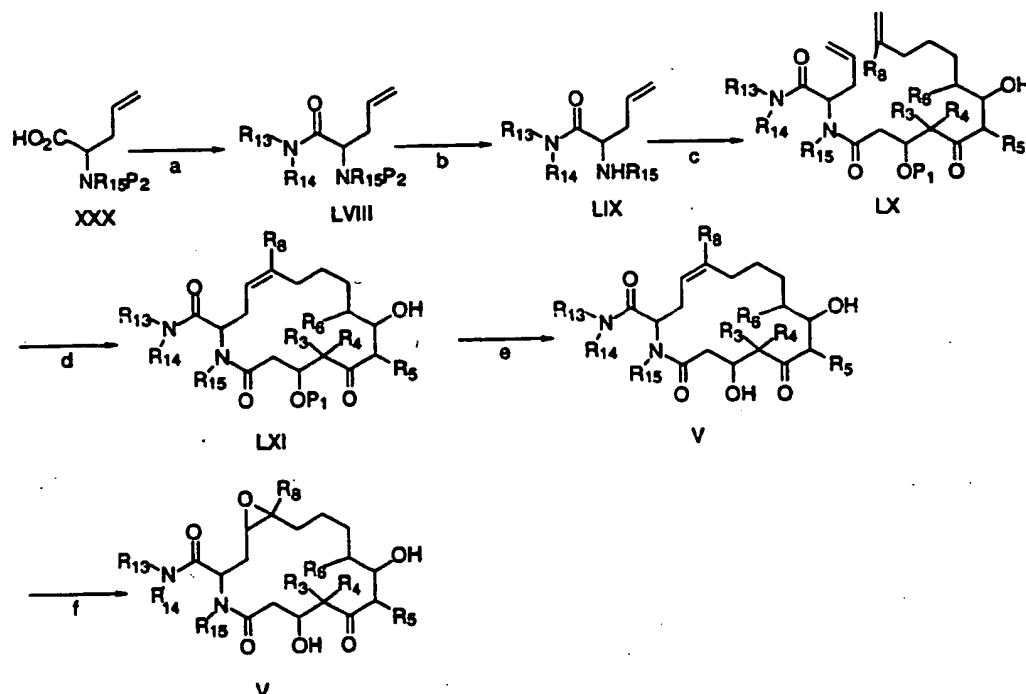


- and D is selected from the group consisting of NR₂₈R₂₉, NR₃₀COR₃₁, and saturated heterocycle (i.e., piperidinyl, morpholinyl, piperazinyl, etc.) can be prepared from a compound of formula V as shown in Scheme 10. A compound of formula V can be converted to a compound of formula LV by protection of the hydroxyl groups with suitable protecting groups such as t-butyldimethylsilyl. A compound of formula LVI can be prepared from a compound of formula LV by ozonolysis.
- 15 Treatment of a compound of formula LVI with an amine and a reducing agent such as sodium triacetoxyboro-hydride provides a compound of formula LVII. Removal of the protecting groups from a compound of formula LVII, with for example hydrogen fluoride, provides a compound of formula V where X is oxygen, W is NR₁₅ or oxygen, and G

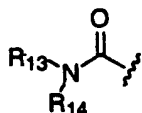
- 20 is



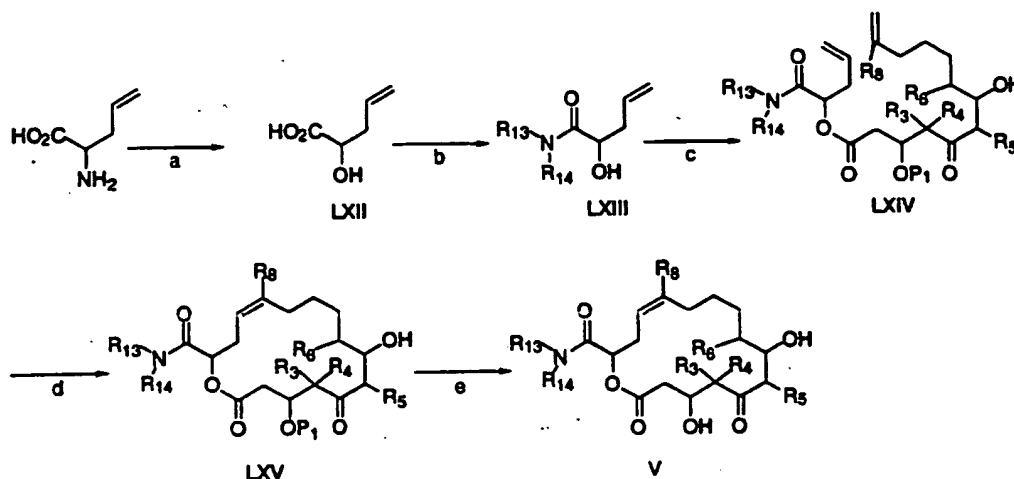
Scheme 11



5 A compound of formula V where W is NR_{15} , X is oxygen, and G is

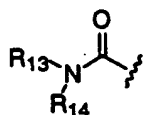


can be prepared as outlined in Scheme 11. A compound of formula LVIII can be prepared from a compound of formula XXX by treatment with an amine and standard amide bond coupling agents such as EDCI and HOBT. A compound of formula LX can be prepared from a compound of formula LVIII by N-deprotection, using for example trifluoroacetic acid when P₂ is a t-butyloxycarbonyl group, followed by coupling of compounds of formula LIX and XIII using standard amide bond coupling agents such as EDCI and HOBT. A compound of formula LXI can be prepared from a compound of formula LX by ring-closing metathesis. A compound of formula V can be prepared from a compound of formula LXI following methods described in Scheme 1.

Scheme 12

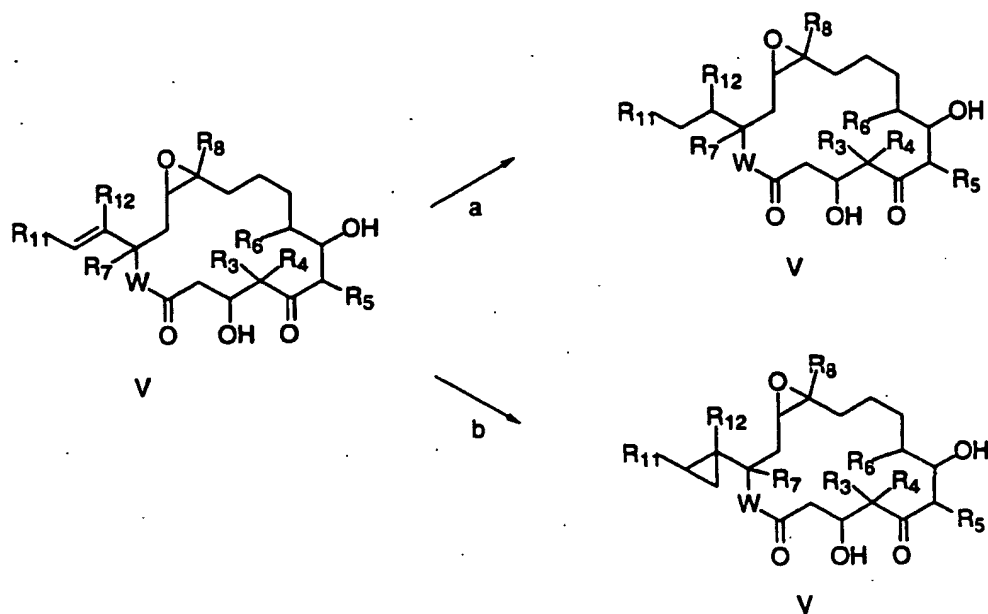
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A compound of formula V where W is oxygen, X is oxygen, and G is

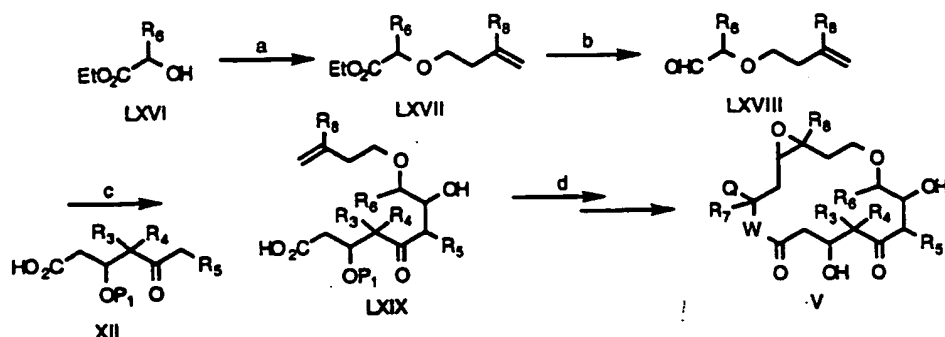


can be prepared as outlined in Scheme 12. A compound of formula LXII
 10 can be prepared from allylglycine by treatment with nitrous acid. A
 compound of formula LXIII can be prepared from a compound of
 formula LXII by treatment with an amine and standard amide bond
 coupling agents such as EDCI and HOBT. A compound of formula
 LXIV can be prepared from compounds of formula LXIII and XIII
 15 using standard amide bond coupling agents such as EDCI and HOBT.
 A compound of formula LXV can be prepared from a compound of
 formula LXIV by ring-closing metathesis. A compound of formula V
 can be prepared from a compound of formula LXV following methods
 described in Scheme 1.

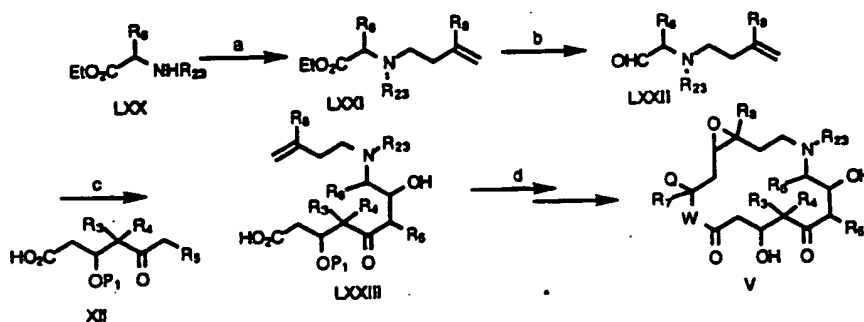
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Scheme 13

- Compounds of formula V where G is a 1,2-disubstituted ethyl
- 5 group can be prepared from a compound of formula V where G is a 1,2-disubstituted ethylene group by hydrogenation with a catalyst such as palladium on carbon, as shown in Scheme 13. Furthermore,
- compounds of formula V where G is a 1,2-disubstituted cyclopropyl
- 10 group can be prepared from a compound of formula V where G is a 1,2-disubstituted ethylene group by cyclopropanation with diiodomethane and zinc-copper couple, as shown in Scheme 4.

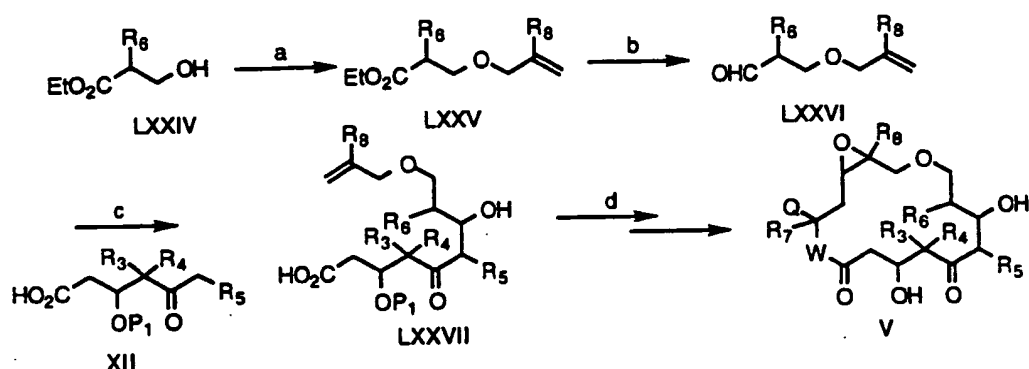
Scheme 14

- 5 A compound of formula V where Z_1 is oxygen can be prepared as shown in Scheme 14. A compound of formula LXVII can be prepared from a α -hydroxy ester LXVI and a 3-buten-1-yl-trifluoromethanesulfonate (or with an 3-butenyl bromide and silver triflate). A compound of formula LXVII can be reduced with a reducing
- 10 agent such as diisobutylaluminum hydride to provide a compound of formula LXVIII. Alternatively, a compound of formula LXVIII can be obtained from a compound of formula LXVII by a two step procedure involving reduction with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXVIII can be
- 15 substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXIX. Further elaboration of LXIX as described above provides a compound of formula V where Z_1 is oxygen.

Scheme 15

Similarly, a compound of formula V where Z_1 is NR_{23} can be prepared as shown in Scheme 15. A compound of formula LXXI can be prepared from a α -amino ester LXX and a 3-buten-1-yl-bromide. A compound of formula LXXI can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXXII. Alternatively, a compound of formula LXXII can be obtained from a compound of formula LXXI by a two step procedure involving reduction with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXXII can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXXIII. Further elaboration of LXXIII as described above provides a compound of formula V where Z_1 is NR_{23} .

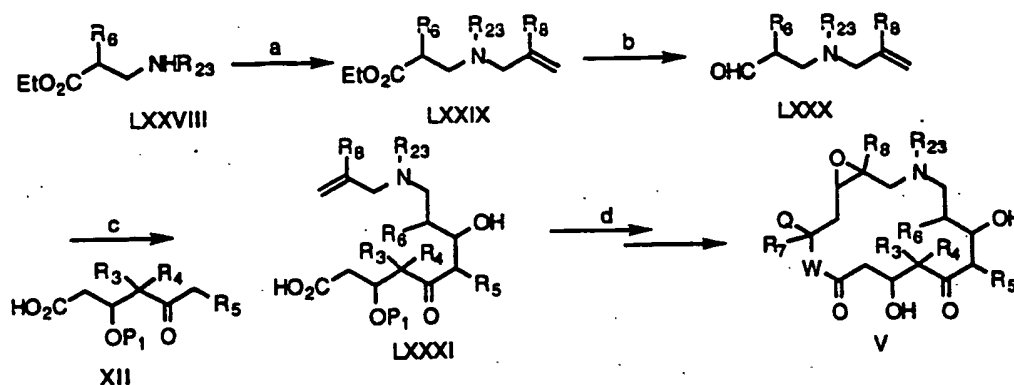
Scheme 16



A compound of formula V where Z_2 is oxygen can be prepared as shown in Scheme 16. A compound of formula LXXV can be prepared from a β -hydroxy ester LXXIV and an allylating agent such as allylbromide (or an allyl bromide and silver triflate). A compound of formula LXXV can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXXVI. Alternatively, a compound of formula LXXVI can be obtained from a compound of formula LXXV by a two step procedure involving reduction

with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXXVI can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXXVII. Further elaboration of LXXVII as described above provides a compound of formula V where Z₂ is oxygen.

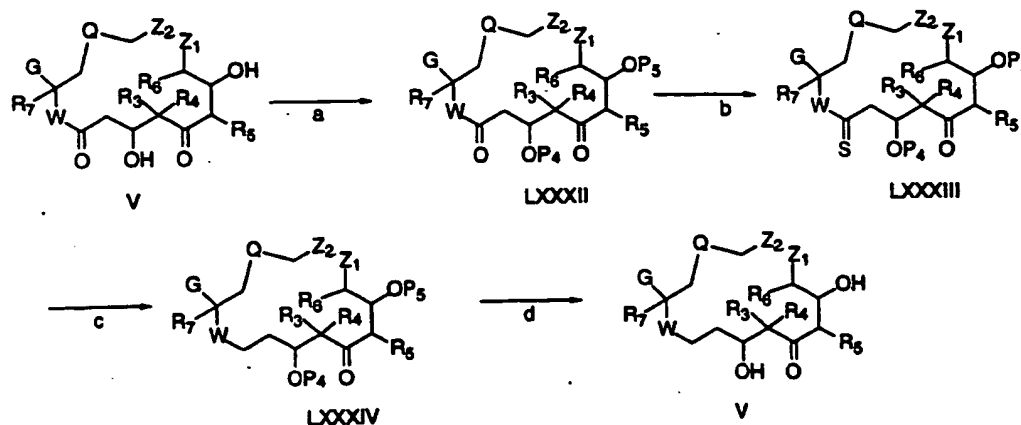
Scheme 17



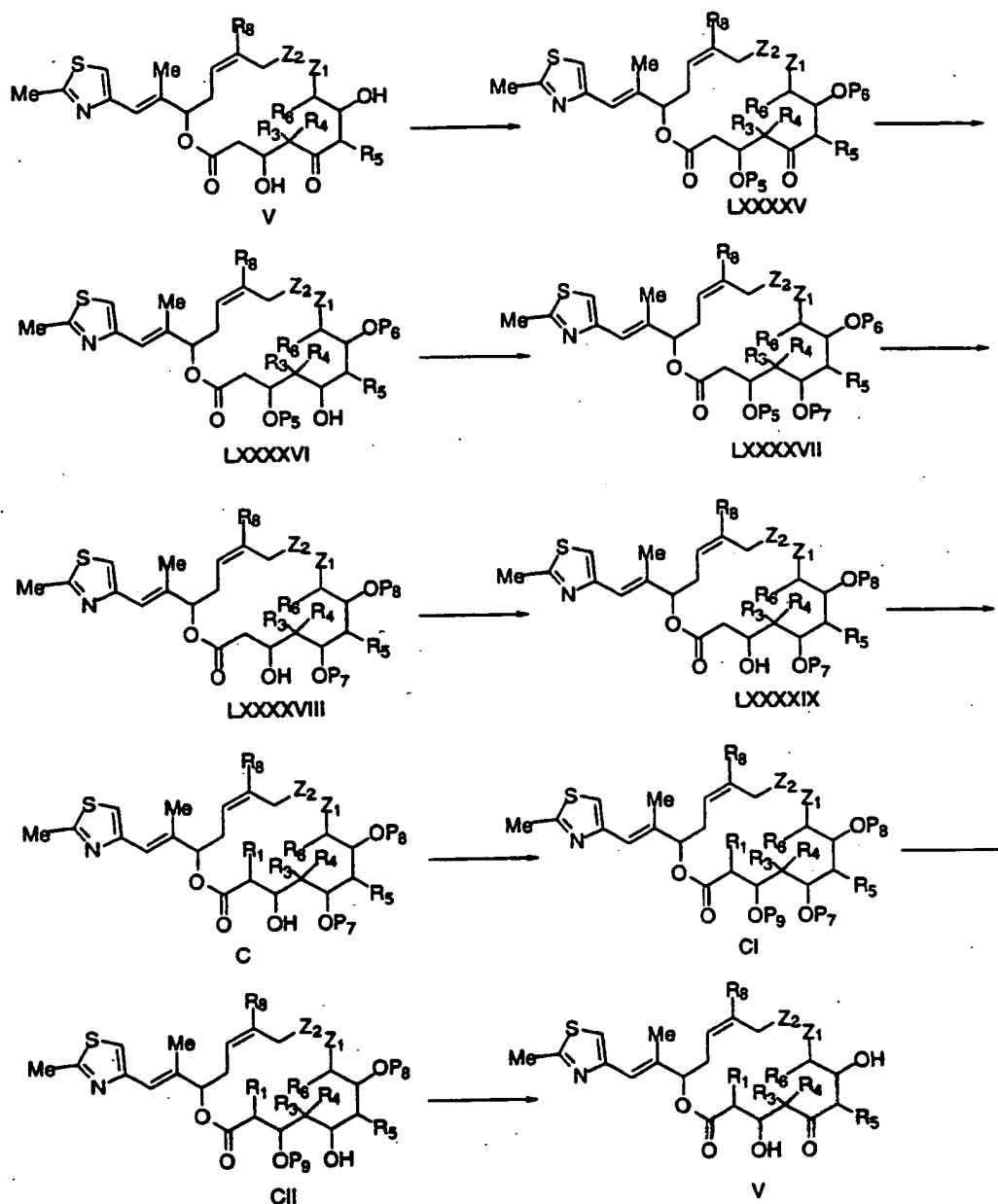
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Similarly, a compound of formula V where Z₂ is NR₂₃ can be prepared as shown in Scheme 17. A compound of formula LXXIX can be prepared from a beta-amino ester LXXVIII and an allylating agent such as allylbromide. A compound of formula LXXIX can be reduced with a reducing agent such as diisobutylaluminum hydride to provide a compound of formula LXXX. Alternatively, a compound of formula LXXX can be obtained from a compound of formula LXXIX by a two step procedure involving reduction with lithium borohydride and oxidation with pyridinium chlorochromate. This compound of formula LXXX can be substituted for a compound of formula XIV in Scheme 1 to give a compound of formula LXXXI. Further elaboration of LXXXI as described above provides a compound of formula V where Z₂ is NR₂₃.

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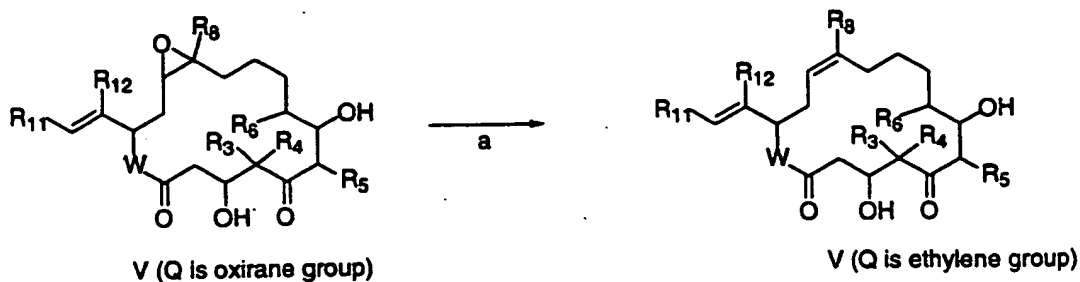
Scheme 18

- A compound of formula V where W is oxygen or NR_{15} and Y is H,H can
 5 be prepared as shown in Scheme 18. A compound of formula V can be
 converted to a compound of formula LXXXII, where P_4 and P_5 are
 hydroxyl protecting groups, by treatment with a reagent such as t-
 butyldimethylsilyltriflate. A compound of formula LXXXIII can be
 prepared from a compound of formula LXXXII by treatment with
 10 Lawesson's reagent. A compound of formula LXXXIV can be prepared
 from a compound of formula LXXXIII by using a reducing agent such
 as tri-n-butyltin hydride when W is oxygen or by treatment with methyl
 iodide and sodium borohydride when W is NR_{15} . Removal of the
 protecting groups from a compound of formula LXXXIV, using for
 15 example hydrogen fluoride when P_4 and P_5 are silyl groups, provides a
 compound of formula V where W is oxygen or NR_{15} and Y is H,H.

Scheme 19

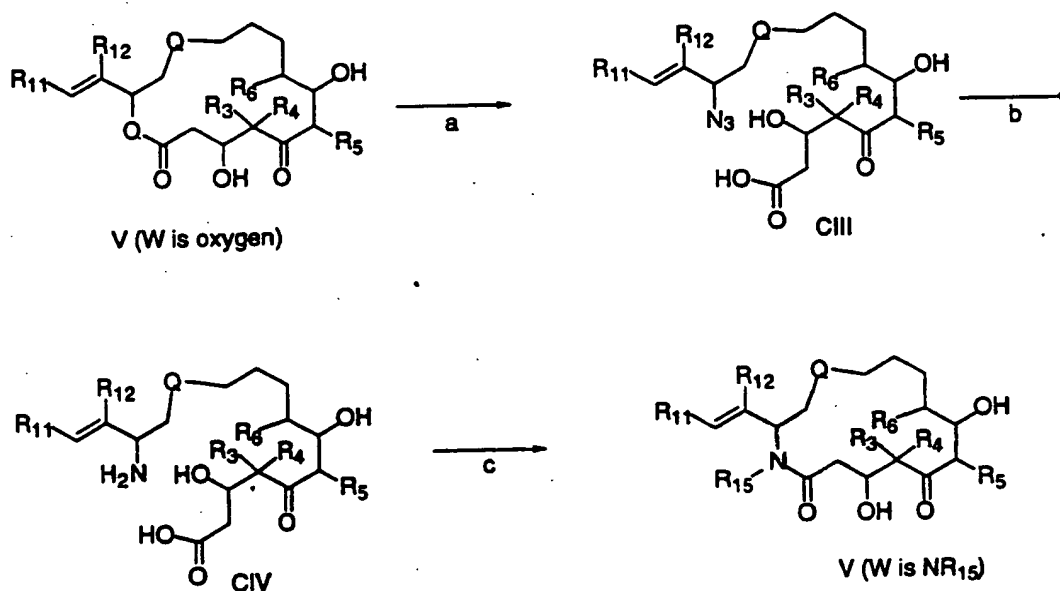
A compound of formula **V** where W and Y are oxygen, and R_1 is alkyl or substituted alkyl can be prepared as shown in Scheme 19. A compound of formula **V** can be protected to give a compound of formula **LXXXV**, where P_5 and P_6 are hydroxyl protecting groups, by treatment with a reagent such as *t*-butyldimethylsilyl trifluoromethanesulfonate. A

compound of formula LXXXVI can be prepared from a compound of formula LXXXV by treatment with a reducing agent such as sodium borohydride. A compound of formula LXXXVII can be prepared from a compound of formula LXXXVI by protection of the hydroxyl group, where P_7 is for example p-methoxybenzyl, using p-methoxybenzyl trichloroacetimidate. Removal of the protecting groups P_5 and P_6 of a compound of formula LXXXVII using, for example, hydrogen fluoride in pyridine when P_5 and P_6 are t-butyldimethylsilyl groups provides a compound of formula LXXXVIII which then can be selectively protected using for example t-butyldimethylsilyl chloride to give a compound of formula LXXXIX where P_8 is a t-butyldimethylsilyl group. A compound of formula C can be prepared from a compound of formula LXXXIX by treatment with a base such as lithium diisopropylamide followed by treatment with an alkylating agent such as methyl iodide. A compound of formula C can be protected to give a compound of formula CI, where P_9 is a hydroxyl protecting group, by treatment with a reagent such as t-butyldimethylsilyl trifluoromethanesulfonate. A compound of formula CII can be prepared from a compound of formula CI by removal of the P_7 group using, for example, DDQ when P_7 is a p-methoxybenzyl group. A compound of formula V, where W and Y are oxygen, and R_1 is alkyl or substituted alkyl, can be prepared from a compound of formula CII by oxidation using, for example, TPAP/NMO followed by removal of the protecting groups using, for example, hydrogen fluoride when P_5 and P_6 are silyl groups. This compound of formula V can be further oxidized with dimethyldioxirane as shown in Scheme 1 to provide the corresponding epoxide compound of formula V.

Scheme 20

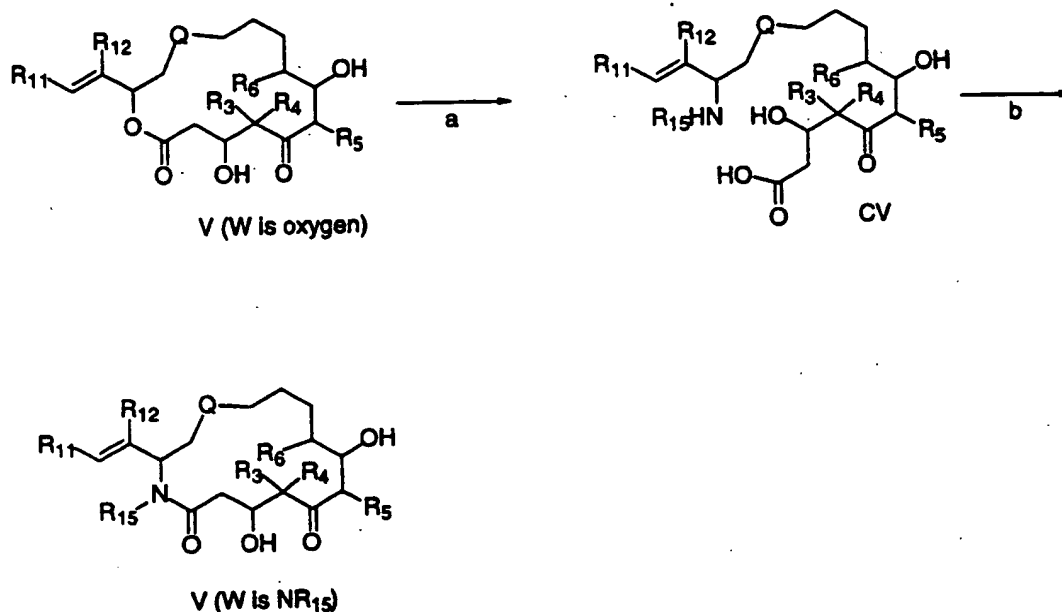
- 5 A compound of formula V where X is oxygen and Q is an olefin can be prepared from a compound of formula V where X is oxygen and Q is an oxirane ring by treatment with a reactive metallocene such as titanocene, zirconocene or niobocene as shown in Scheme 20 (see for example R. Schobert and U. Hohlein, *Synlett* (1990), 465-466.).

10

Scheme 21

- 15 A compound of formula V where X is oxygen and W is NR₁₅, where R₁₅ is hydrogen, can be prepared from a compound of formula V where both X and W are oxygen as shown in Scheme 21. A compound of

- formula CIII can be prepared from a compound of formula V where both X and W are oxygen by formation of pi-allylpalladium complex using, for example, palladium tetrakis(triphenylphosphine) followed by treatment with sodium azide (see, for example: Murahashi, S.-I.; et. al. *J. Org. Chem.* 1989, 54, 3292). Subsequent reduction of a compound of formula CIII with a reducing agent such as triphenylphosphine provides a compound of formula CIV. A compound of formula V where X is oxygen and W is NR_{15} , where R_{15} is hydrogen, can be prepared from a compound of formula CIV by macrolactamization using, for example, diphenylphosphoryl azide or bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP).

Scheme 22

- A compound of formula V where X is oxygen and W is NR_{15} , where R_{15} is alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl, heterocyclo, O-alkyl, O-substituted alkyl, can be prepared from a compound of formula V where both X and W are oxygen as shown in Scheme 22. A compound of formula CV can be prepared from a compound of formula V where both X and W are oxygen by formation of pi-allylpalladium complex using, for example, palladium

tetrakis(triphenylphosphine) followed by treatment with a primary amine. A compound of formula V where X is oxygen and W is NR_{15} , where R_{15} is alkyl, substituted alkyl, aryl, heteroaryl, cycloalkyl, heterocyclo, OH, O-alkyl, O-substituted alkyl, can be prepared from a compound of formula V by macrolactamization using, for example, diphenylphosphoryl azide or bromotripyrrolidinophosphonium hexafluorophosphate (PyBroP). In the case where R_{15} is OH, it may be necessary to remove a protecting group such as *t*-butyldimethylsilyl from an intermediate where R_{15} is O-*t*-butyldimethylsilyl.

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The *in vitro* assessment of biological activity of the compounds of Formula V was performed as follows:

In vitro Tubulin Polymerization. Twice cycled (2X) calf brain tubulin was prepared following the procedure of Williams and Lee (see Williams, R.C., Jr., and Lee, J. C. Preparation of tubulin from brain. Methods in Enzymology 85, Pt. D: 376-385, 1982) and stored in liquid nitrogen before use. Quantification of tubulin polymerization potency is accomplished following a modified procedure of Swindell, et al., (see Swindell, C.S., Krauss, N.E., Horwitz, S.B., and Ringel, I. Biologically active taxol analogues with deleted A-ring side chain substituents and variable C-2' configurations. J. Med. Chem. 34: 1176-1184, 1991). These modifications, in part, result in the expression of tubulin polymerization potency as an effective concentration for any given compound. For this method, different concentrations of compound in polymerization buffer (0.1M MES, 1mM EGTA, 0.5 mM MgCl_2 , pH 6.6) are added to tubulin in polymerization buffer at 37° in microcuvette wells of a Beckman (Beckman Instruments) Model DU 7400 UV spectrophotometer. A final microtubule protein concentration of 1.0 mg/ml and compound concentration of generally 2.5, 5.0, and 10 μM are used. Initial slopes of OD change measured every 10 seconds were calculated by the program accompanying the instrument after initial and final times of the linear region encompassing at least 3 time points were manually defined.

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Under these conditions linear variances were generally $<10^{-6}$, slopes ranged from 0.03 to 0.002 absorbance unit/minute, and maximum absorbance was 0.15 absorbance units. Effective concentration ($EC_{0.01}$) is defined as the interpolated concentration capable of inducing an initial slope of 0.01 OD/minute rate and is calculated using the formula: $EC_{0.01}$ = concentration/slope. $EC_{0.01}$ values are expressed as the mean with standard deviation obtained from 3 different concentrations. $EC_{0.01}$ values for the compounds in this invention fall in the range 0.01-1000 μ M.

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Cytotoxicity (In-Vitro)

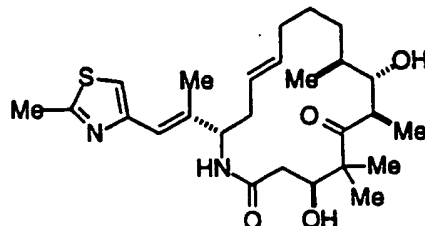
Cytotoxicity was assessed in HCT-116 human colon carcinoma cells by MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphenyl)-2H-tetrazolium, inner salt) assay as reported in T.L. Riss, et. al., "Comparison of MTT, XTT, and a novel tetrazolium compound MTS for in vitro proliferation and chemosensitivity assays.," *Mol. Biol. Cell* 3 (Suppl.):184a, 1992. Cells were plated at 4,000 cell/well in 96 well microtiter plates and 24 hours later drugs were added and serially diluted. The cells were incubated at 37° for 72 hours at which time the tetrazolium dye, MTS at 333 μ g/ml (final concentration), in combination with the electron coupling agent phenazine methosulfate at 25 μ M (final concentration) was added. A dehydrogenase enzyme in live cells reduces the MTS to a form that absorbs light at 492nm which can be quantitated spectrophotometrically. The greater the absorbance the greater the number of live cells. The results are expressed as an IC_{50} , which is the drug concentration required to inhibit cell proliferation (i.e. absorbance at 450nm) to 50% of that of untreated control cells. The IC_{50} values for compounds of this invention fall in the range 0.01 - 1000 nM.

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The following examples illustrate the present invention.

Example 1



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[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione

10 **A. N-[(2-Methyl)-1-propenyl]morpholine.**

To stirring morpholine (165.5 g, 1.9 mol) was added isobutyraldehyde (173 mL, 1.9 mol) at a rate which did not allow the temperature of the reaction to exceed 30 °C. After complete addition, the reaction mixture was stirred at room temperature for 2 h, and then the flask was equipped with a Dean-Stark trap and heated at 160 °C for 20 h. The reaction mixture was then cooled to room temperature, and the flask was equipped with a vigreux column distillation apparatus. Distillation under high vacuum gave 135 g (50%) of Compound A as a clear colorless oil. MS (M+H, 142).

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B. 2,2-Dimethyl-3-oxopentanal.

To a stirring solution of propionyl chloride (44 mL, 0.50 mol) in ether (135 mL) at 0 °C under nitrogen was added a solution of Compound A (69 g, 0.50 mol) in ether (135 mL) over 45 min. After addition was complete, the reaction mixture was stirred at reflux for 2h, and then stirred at room temperature for 16 h. The reaction mixture was filtered, and the filter cake was washed with ether (50 mL). The volatiles were removed *in vacuo*. The residue was taken into H₂O (80 mL) and the solution was adjusted to a pH of 4. Ether was added (80 mL) and the biphasic mixture was stirred for 16 h. The reaction mixture was poured into a separatory funnel, the layers separated, and the aqueous layer

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was extracted with ether (5 x 100 mL). The combined organics were dried (MgSO_4), filtered, and evaporated *in vacuo*. The residue was distilled under high vacuum to give 10.4 g (16%) of Compound B as a clear, colorless oil. MS (M-H, 127).

5

C. 4-*tert*-Butyldimethylsilyloxy-5,5-dimethyl-6-oxo-1-octene.

To a solution of (-)-*B*-methoxydiisopinocampheylborane (25.7 g, 81 mmol) in ether (80 mL) at 0 °C under nitrogen was added 1.0 M allylmagnesium bromide in ether (77 mL, 77 mmol) over 1.5 h. The reaction mixture was stirred at 25 °C for 1 h, and then concentrated *in vacuo*. The residue was extracted with pentane (2 x 150 mL), and the extracts were filtered through Celite under nitrogen. The combined extracts were then evaporated *in vacuo* to give the *B*-allyldiisopinocampheylborane. This material was taken up in ether (200 mL) and cooled to -100 °C under nitrogen. A solution of Compound B (11.42 g, 89 mmol) in ether (90 mL) at -78 °C was then added over a 1 h period. The reaction mixture was stirred for an additional 0.5 h and methanol (1.5 mL) was added. The reaction mixture was brought to room temperature, treated with 3 N NaOH (32 mL) and 30% H_2O_2 (64 mL), and then kept at reflux for 2 h. The reaction mixture was cooled to room temperature, the layers were separated, and the organic phase was washed with H_2O (500 mL). The combined aqueous washes were re-extracted with ether (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL), dried (MgSO_4), filtered, and concentrated *in vacuo*. This residue was taken up in CH_2Cl_2 (250 mL), cooled to 0 °C, and diisopropylethylamine (93 mL, 535 mmol) was added. To the stirring solution was then added *tert*-butyldimethylsilyl trifluoromethanesulfonate (69 g, 260 mmol) slowly as to not increase the temperature above 10 °C. After complete addition, the reaction mixture was poured into H_2O (650 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 650 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexanes followed by 10% EtOAc/hexanes to give 17.2 g (78%) of Compound C as a

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clear, colorless oil. The enantiomeric excess was found to be 94% determined by ^1H NMR analysis of the Mosher's ester of the alcohol. ^{13}C NMR (CDCl_3 , 80 MHz) δ 215.8, 136.1, 116.5, 52.8, 39.0, 31.9, 26.0, 22.4, 20.1, 18.1, 7.6, -3.6, -4.4.

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D. 3-*tert*-Butyldimethylsiloxy-4,4-dimethyl-5-oxoheptanal.

Through a solution of Compound C (10.8 g, 38.0 mmol) in CH_2Cl_2 at -78°C was bubbled O_3 until the solution remained blue (1 h). O_3 was then bubbled through for 15 min followed by N_2 for 30 min after which time the solution became clear. Triphenylphosphine (10 g, 38 mmol) was then added and the reaction mixture was warmed to -35°C and stored for 16 h. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography eluting with 8% EtOAc/hexanes to give 8.9 g (74%) of Compound D as a clear, colorless oil. ^1H NMR (CDCl_3 , 300 MHz) δ 9.75 (m, 1H), 4.53 (t, $J=4.8$ Hz, 1H), 3.40-3.60 (m, 4H), 1.10 (s, 3H), 1.07 (s, 3H), 0.98 (t, $J=7.0$ Hz, 3H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H).

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E. 3-*tert*-Butyldimethylsiloxy-4,4-dimethyl-5-oxoheptanoic acid.

To a solution of Compound D (3.90 g, 13.6 mmol) in *t*-butanol (75 mL) was added 2-methyl-2-butene (5.85 mL, 55.2 mmol), and then a solution of sodium chlorite (4.61 g, 40.8 mmol) and sodium phosphate monobasic (2.81 g, 20.4 mmol) in H_2O (15 mL) was added dropwise at room temperature. The reaction mixture was stirred for 0.5 h and then the solvents were removed *in vacuo*. To the residue was added H_2O (150 mL) followed by extraction with EtOAc (3 x 150 mL). The combined organic extracts were dried (MgSO_4), filtered, and the volatiles were removed *in vacuo*. The residue was purified by flash chromatography eluting with 20% EtOAc/hexanes/1% AcOH to give 3.79 g (92%) of Compound E as a clear, colorless, viscous oil. MS ($M+H$, 303)

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F. (R,R)-N-(2-Hydroxy-1-methyl-2-phenethyl)-N,2-(S)-dimethyl-6-hepteneamide.

A suspension of LiCl (6.9 g, 0.16 mol) and preformed lithium diisopropylamide (Aldrich, 2.0 M solution in heptane/ethylbenzene/THF, 27.6 mL, 55 mmol) in additional THF (70 mL) at -78 °C was treated dropwise with a solution of (R,R)-N-(2-hydroxy-1-methyl-2-phenylethyl)-N-methyl propionamide (6.0 g, 27 mmol, Meyers, A.G. *et al. J. Am. Chem. Soc.* 1994, 116, 9361) in THF (30 mL) over 10 min. The bright yellow, reaction mixture was stirred at -78 °C (1 h), at 0 °C (15 min), and at 25 °C (5 min) before being recooled to 0 °C and treated with a solution of 5-bromo-1-pentene (4.8 mL, 40 mmol) in THF (5 mL). The reaction mixture was stirred at 0 °C (24 h), poured into saturated aqueous NH₄Cl (100 mL) and EtOAc (100 mL). The two phases were separated and the aqueous phase was further extracted with EtOAc (3 x 100 mL). The organic extracts were combined, washed with saturated aqueous NaCl (200 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 4.0 x 25 cm, 2 % MeOH-CHCl₃) afforded Compound F (6.9 g, 88 %) as a pale yellow oil. MS (ESI⁺): 290 (M+H)⁺; MS(ESI): 288.2 (M-H).

G. (S)-2-Methyl-6-heptenol.

A 250 mL round-bottom flask at 0 °C was charged sequentially with pyrrolidine (2.6 mL, 30 mmol) and BH₃-THF complex (1.0 M in THF, 31 mL, 30 mmol). The borane-pyrrolidine complex was warmed to 25 °C (1 h), recooled to 0 °C, and treated with *n*-butyllithium (1.6 M in hexane, 19 mL, 30 mmol) dropwise over 30 min while carefully maintaining an internal temperature below 5.5 °C. The reaction mixture was stirred at 0 °C for an additional 30 min before a solution of Compound F (3.0 g, 10 mmol) in THF (23 mL) was added dropwise over 10 min. The reaction mixture was stirred at 25 °C (6 h) before being quenched by the dropwise addition of aqueous 3 N HCl (25 mL). The reaction mixture was then poured into aqueous 1 N HCl (200 mL) and extracted with Et₂O (4 x 80 mL). The combined organics were washed with a 1:1 solution of saturated aqueous NaCl - aqueous 1 N HCl (2 x 150 mL) and concentrated *in vacuo*. An aqueous solution of NaOH (1 N, 200

mL) was added to the residue and the suspension was stirred for 30 min. The mixture was extracted with Et₂O (3 x 100 mL) and the combined ether layers were washed with a 1:1 solution of saturated aqueous NaCl - aqueous 1 N NaOH (2 x 200 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 4.0 x 25 cm, 15-25 % Et₂O-pentane gradient elution) afforded Compound G (1.26 g, 95 %) as a colorless oil. $[\alpha]_D^{25}$ -11 (c 12, CH₂Cl₂).

H. (S)-2-Methyl-6-heptenal

A solution of Compound G (0.24 g, 1.9 mmol) in CH₂Cl₂ (6 mL) was treated with pyridinium chlorochromate (0.61 g, 2.8 mmol) and the reaction mixture was stirred at 25 °C for 5 h. The resulting dark brown viscous slurry was passed through a silica gel-Celite plug (Celite 1.0 x 1 cm on top of SiO₂, 1.0 x 5 cm, eluting with 50 mL of CH₂Cl₂). The solvent was removed *in vacuo* to afford crude Compound H (0.15 g, 63 %) as a colorless oil, which was sufficiently pure to use in subsequent reactions. ¹H NMR (300 MHz, CD₂Cl₂) δ 9.62 (s, 1H), 5.88-5.68 (m, 1H), 5.13-4.92 (m, 2H), 2.37-2.24 (m, 1H), 2.15-2.05 (m, 2H), 1.62-1.78 (m, 1H), 1.51-1.32 (m, 3H), 1.07 (d, 3H, *J* = 7.0 Hz).

I. (3S,6R,7S,8S)-3-*tert*-Butyldimethylsiloxy-4,4,6,8-tetramethyl-7-hydroxy-5-oxo-12-tridecenoic acid

To a preformed LDA solution (Aldrich, 2.0 M solution in heptane/ethylbenzene/THF, 3.8 mL, 7.6 mmol) in additional THF (25 mL) at -78 °C was added a solution of Compound E (1.0 g, 3.4 mmol) in THF (5 mL) dropwise over 3 min. The reaction mixture was stirred at -78 °C (10 min), warmed to -40 °C (20 min), and re-cooled to -78 °C before Compound H (0.56 g, 4.4 mmol) in THF (5 mL) was added. The reaction mixture was warmed to -40 °C, stirred for 1 h, and diluted with saturated aqueous NH₄Cl (50 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 2.5 x 20 cm, 2-5 % MeOH-CHCl₃, gradient elution) followed by HPLC (YMC S-10, ODS, 30 x 500 mm column, eluting with MeOH at a flow rate of 20 mL/min) separation afforded the desired *syn*-aldol product Compound I

(0.60 g, 43 %) and an undesired diastereomer (0.32 g, 22 %) along with starting Compound E (~10%).

MS (ESI⁺): 879.3 (2M+Na)⁺, 451.2 (M+ Na)⁺, 429.2 (M+H)⁺; MS(ESI⁻): 427.3 (M-H)⁻.

- 5 Stereochemistry was confirmed by direct comparison of both the ¹³C and ¹H NMRs of the subsequent ester derivative (used in the synthesis of Epothilone C) to the same intermediate previously described by K.C. Nicolaou *et al. Angew. Chem. Int. Ed. Engl.* 1997, 36, 166.

10 **J. (S)-2-[N-[(*tert*-Butyloxy)carbonyl]amino]-4-pentenoic acid.**

- A solution L-2-amino-4-pentenoic acid (NovaBiochem, 3.0 g, 26 mmol) in THF-H₂O (1:1, 200 mL) at 0 °C was treated sequentially with NaHCO₃ (6.6 g, 78 mmol) and di-*tert*-butyl dicarbonate (10.4 g, 1.8 mmol). The reaction mixture was warmed to 25 °C and stirred for 16 h. The pH of the mixture was adjusted to 4 by the careful addition of saturated aqueous citric acid at 0 °C, and the mixture was extracted with EtOAc (4 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl (75 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 4.0 x 6 cm, 5-10 % MeOH-CHCl₃, gradient elution) afforded Compound J (5.5 g, 99 %) as a colorless oil. MS(ESI⁻): 429.3 (2M-H)⁻, 214.1 (M-H)⁻.

K. (S)-2-[N²-[(*tert*-Butyloxy)carbonyl]amino]-N-methoxy-N-methyl-4-penteneamide.

- 25 A solution Compound J (2.9 g, 13 mmol) in CHCl₃ (55 mL) at 0 °C was treated sequentially with *N,O*-dimethylhydroxylamine hydrochloride (1.4 g, 15 mmol), 1-hydroxybenzotriazole (2.0 g, 15 mmol), 4-methylmorpholine (4.4 mL, 40 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.4 g, 18 mmol). The reaction mixture was gradually warmed to 25 °C, stirred for 16 h, and diluted with H₂O (100 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (3 x 75 mL). The combined organic phases were washed with aqueous 5 % HCl (100 mL), saturated aqueous NaHCO₃ (100 mL), saturated aqueous NaCl (100 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 3.0 x 20 cm, 25-50 % EtOAc-hexan gradient elution) afforded Compound K (2.5 g, 71%)

as a colorless oil. MS (ESI⁺): 258.9 (M+H)⁺, 202.9 (M-isobutylene), 158.9 (M-BOC); MS(ESI⁻): 257.2 (M-H)⁻.

L. (S)-3-[N-[(*tert*-Butyloxy)carbonyl]amino]-5-hexen-2-one.

- 5 A solution of Compound K (2.5 g, 1.0 mmol) in THF (65 mL) at 0 °C was treated with methylmagnesium bromide (3.0 M in Et₂O, 8.1 mL, 2.4 mmol). The reaction mixture was stirred at 0 °C (2.5 h) and carefully poured into saturated aqueous NH₄Cl (100 mL). The two layers were separated and the aqueous phase was extracted with EtOAc (3 x 75 mL).
- 10 The combined organic extracts were washed with saturated aqueous NH₄Cl (75 mL), H₂O (75 mL), saturated aqueous NaCl (75 mL), dried (MgSO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 3.0 x 20 cm, 10-25 % EtOAc-hexane gradient elution) afforded (S)-2-[N-[(*tert*-Butyloxy)carbonyl]amino]-5-hexene-2-one (2.2 g, 67%) as a colorless oil.
- 15 MS (ESI⁺): 213.9 (M+H)⁺, 157.9 (M-isobutylene), 113.9 (M-BOC); MS(ESI⁻): 212.2 (M-H)⁻.

M. (S)-4-[3-[N-[(*tert*-Butyloxy)carbonyl]amino]-2-methyl-1(E),5-hexadienyl]-2-methylthiazole.

- 20 A solution of 2-methyl-4-thiazolylmethyl diphenylphosphine oxide (2.5 g, 8.0 mmol, Danishefsky *et al.* *J. Org. Chem.* 1996, 61, 7998) in THF (38 mL) at -78 °C was treated with *n*-butyllithium (1.6 M in hexane, 5.2 mL, 8.4 mmol) dropwise over 5 min. The resulting brilliant orange mixture was stirred for 15 min at -78 °C, and treated with a
- 25 solution of Compound L (0.81 g, 3.8 mmol) in THF (5 mL). After 10 min at -78 °C, the cooling bath was removed and the reaction mixture was allowed to warm to 25 °C (2 h). The mixture was poured into saturated aqueous NH₄Cl (50 mL) and the two layers were separated. The aqueous phase was extracted with Et₂O (3 x 50 mL) and the combined organic
- 30 extracts were washed successively with H₂O (75 mL), saturated aqueous NaHCO₃ (75 mL), saturated aqueous NaCl (75 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 4.0 x 30 cm, 10-20 % EtOAc-hexane gradient elution) afforded Compound M (0.23 g, 18%) as a colorless oil along with recovered starting ketone (20-30%). MS
- 35 (ESI⁺): 309.1 (M+H)⁺, 253.0 (M-isobutylene); MS(ESI⁻): 307.3 (M-H)⁻.

N. (S)-4-(3-Amino-2-methyl-1(E),5-hexadienyl)-2-methylthiazole.

Compound M (0.15 g, 0.49 mmol) was treated with 4.0 N HCl in 1,4-dioxane (5 mL) at 0 °C (30 min) under Ar. The volatiles were removed *in vacuo*, and the resulting white foam was dissolved in cold saturated aqueous NaHCO₃ (3 mL). The solution was extracted with EtOAc (4 x 10 mL), and the combined EtOAc layers were dried (Na₂SO₄) and concentrated *in vacuo*. Flash chromatography (SiO₂, 1.0 x 5 cm, 5-10 % MeOH-CHCl₃, gradient elution) afforded Compound N (88 mg, 88 %) as a colorless oil. MS (ESI⁺): 209.0 (M+H)⁺; MS(ESI): 207.2 (M-H).

O. (3S,6R,7S,8S)-N-(S)-[1-(2-Methyl-4-thiazolyl)-2-methyl-1(E),5-hexadien-3-yl]-3-*tert*-butyldimethylsiloxy-4,4,6,8-tetramethyl-7-hydroxy-5-oxo-12-trideceneamide.

A solution of Compound M (88 mg, 0.42 mmol) in DMF (1.3 mL) at 0 °C was treated sequentially with Compound I (0.15 g, 0.35 mmol), 1-hydroxybenzotriazole (49 mg, 0.36 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.10 g, 0.52 mmol). The reaction mixture was gradually warmed to 25 °C, stirred for 15 h, and diluted with H₂O (3 mL). The mixture was extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with aqueous 5 % HCl (10 mL), saturated aqueous NaHCO₃ (10 mL), saturated aqueous NaCl (10 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash chromatography (SiO₂, 1.5 x 20 cm, 2.5 % MeOH-CHCl₃) afforded Compound O (0.17 g, 77 %) as a white foam. MS (ESI⁺): 619.3 (M+H)⁺.

P. [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4-*tert*-Butyldimethylsiloxy-8-hydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione.

A solution of Compound O (17 mg, 27 μmol) in degassed benzene (8.0 mL) was treated with Grubb's catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium dichloride, Strem Chemicals, 11 mg, 14 μmol) under Ar. The reaction mixture was stirred at 25 °C for 15 h and treated again with an additional portion of catalyst (5.0 mg, 4.5 μmol). After 7 additional hours, the benzene was removed *in vacuo*, and the black viscous residue was passed through a pad of silica gel (1.0 x 3 cm) eluting with Et₂O (25 mL). The eluent was concentrated *in vacuo*

to afford a separable 5:1 (*E/Z*) mixture of geometric isomers. PTLC (SiO₂, 1 mm plate, 2 elutions with a 1:1:1 solution of hexane-toluene-ethyl acetate) afforded the *E*-isomer Compound P (5.1 mg, 34 %) and the corresponding *Z*-isomer (1.0 mg, 6.7 %). For Compound P: MS (ESI⁺): 1181.7 (2M+H)⁺, 591.4 (M+H)⁺. For the *Z*-isomer: MS (ESI⁺): 1181.5 (2M+H)⁺, 613.2 (M+Na)⁺, 591.2 (M+H)⁺; MS (ESI⁻): 589.3 (M-H)⁻.

Q. [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione.

To a 1 dram vial charged with Compound P (2.3 mg, 3.9 mmol) in CH₂Cl₂ (0.4 mL) at 0 °C was added trifluoroacetic acid (0.1 mL). The reaction mixture was sealed under a blanket of Ar and stirred at 0 °C. After 4 h, the volatiles were removed under a constant stream of Ar at 0 °C. Saturated aqueous NaHCO₃ (1 mL) and EtOAc (1 mL) were added to the residue and the two layers were separated. The aqueous phase was extracted with EtOAc (4 x 1 mL), and the combined EtOAc layers were dried (Na₂SO₄) and concentrated *in vacuo*. PTLC (SiO₂, 20 x 10 x 0.025 cm, eluting with 5 % MeOH-CHCl₃) afforded [4S-[4R*,7S*,8S*,9R*,15R*(E)]]-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(E)-cyclohexadecene-2,6-dione (1.3 mg, 68 %) as a white film. MS (ESI⁺): 953.5 (2M+H)⁺, 477.3 (M+H)⁺; MS (ESI⁻): 475.5 (M-H)⁻.

Example 2

The following compounds can be made following the reaction schemes previously disclosed:

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;
- 5 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;
- 10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxa-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 30 1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 35 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 5 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 10 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7,9,13-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;

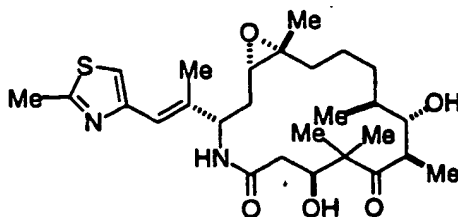
- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7, 9-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 35 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;

- [1S-[1R,3R,7R,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
- 5 [1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
- 10 [4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;
- [4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide.
- 15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.
- 20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.

25

30

Example 3



5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

A. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-12,13-epoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-10 16-heptadecenoic acid.

A solution of epothilone B (0.35 g, 0.69 mmol) in degassed THF (4.5 mL) was treated with a catalytic amount (80 mg, 69 mmol) of tetrakis(triphenylphosphine) palladium (0) and the suspension was stirred at 25 °C, under Ar for 30 min. The resulting bright yellow, 15 homogeneous solution was treated all at once with a solution of sodium azide (54 mg, 0.83 mmol) in degassed H₂O (2.2 mL). The reaction mixture was warmed to 45 °C for 1 h, diluted with H₂O (5 mL) and extracted with EtOAc (4 x 7 mL). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The 20 residue was purified by flash chromatography (SiO₂, 3.0 x 15 cm, 95:5.0:0.5 CHCl₃-MeOH-AcOH) to afford Compound A (0.23 g, 61 %) as a colorless oil. MS (ESI⁺): 551 (M+H)⁺; MS(ESI⁻): 549 (M-H)⁻.

B. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-12,13-epoxy-4,4,6,8,12,16-hexamethyl-7-hydroxy-17-(2-methyl-4-thiazolyl)-5-oxo-16-heptadecenoic acid.

A solution of Compound A (0.23 g, 0.42 mmol) in THF (4.0 mL) was
5 treated with H₂O (23 mL, 1.25 mmol) and polymer supported
triphenylphosphine (Aldrich, polystyrene cross-linked with 2 % DVB, 0.28
g, 0.84 mmol) at 25 °C. The resulting suspension was stirred at 25 °C
under Ar (32 h), filtered through a Celite pad and concentrated *in vacuo*.
The residue was purified by flash chromatography (SiO₂, 1.5 x 10 cm,
10 95:5.0:0.5 to 90:10:1.0 CHCl₃-MeOH-AcOH gradient elution) to afford
Compound B (96 mg, 44 %) as a colorless oil. MS (ESI⁺): 525.2 (M+H)⁺;
MS(ESI⁻): 523.4 (M-H)⁻.

Alternatively, to a 25 mL round-bottom flask charged with
Compound A (0.26 g, 0.47 mmol) and PtO₂ (0.13 g, 50 wt %) was added
15 absolute EtOH under Ar. The resulting black mixture was stirred under
one atmosphere of H₂ for 10 h, after which time the system was purged
with N₂ and an additional portion of PtO₂ (65 mg, 25 wt %) was added.
Once again the reaction mixture was stirred under a blanket of H₂ for 10 h.
The system was then purged with N₂, and the reaction mixture was filtered
20 through a Celite pad eluting with CH₂Cl₂ (3 x 25 mL). The solvents were
removed *in vacuo* and the residue was purified as described above to afford
Compound B (0.19 g, 75 %).

Alternatively, a solution of Compound A (20 mg, 36 mmol) in THF
(0.4 mL) was treated with triphenylphosphine (19 mg, 73 mmol) under Ar.
25 The reaction mixture was warmed to 45 °C, stirred for 14 h and cooled to
25 °C. The resulting iminophosphorane was treated with ammonium
hydroxide (28 %, 0.1 mL) and once again the reaction mixture was warmed

to 45 °C. After 4 h, the volatiles were removed *in vacuo* and the residue was purified as described above to afford Compound B (13 mg, 70 %).

C. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-

5 8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.
A solution of Compound B (0.33 g, 0.63 mmol) in degassed DMF (250 mL) was treated with solid NaHCO₃ (0.42 g, 5.0 mmol) and diphenylphosphoryl azide (0.54 mL, 2.5 mmol) at 0°C under Ar. The resulting suspension was
10 stirred at 4 °C for 24 h, diluted with phosphate buffer (250 mL, pH=7) at 0°C and extracted with EtOAc (5 x 100 mL). The organic extracts were washed with 10% aqueous LiCl (2 x 125 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The residue was first purified by flash chromatography (SiO₂, 2.0 x 10 cm, 2-5 % MeOH-CHCl₃ gradient elution)
15 and then repurified using a Chromatotron (2 mm SiO₂, GF rotor, 2-5% MeOH-CHCl₃ gradient elution) to afford the title compound (0.13 g, 40%) as a colorless oil: ¹H NMR (CDCl₃, 400 MHz) δ 6.98 (s, 1 H), 6.71 (d, 1H, NH, *J* = 8.1 Hz), 6.56 (s, 1 H), 4.69-4.62 (m, 1 H), 4.18-4.12 (m, 1 H), 4.01-3.96 (m, 1 H), 3.86 (s, 1 H), 3.38-3.34 (m, 1 H), 2.82 (dd, 1 H, *J* = 5.6, 6.0
20 Hz), 2.71 (s, 3 H), 2.58 (s, 1 H), 2.43 (dd, 1 H, *J* = 9.0, 14.5 Hz), 3.34 (dd, 1 H, *J* = 3.0, 14.5 Hz), 2.14 (s, 3 H), 2.05-1.92 (m, 2 H), 1.82-1.41 (a series of multiplets, 7 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.18 (d, 3 H, *J* = 6.8 Hz), 1.14 (s, 3 H), 1.00 (d, 3 H, *J* = 6.8 Hz); MS (ESI⁺): 507.2 (M+H)⁺; MS(ESI⁻): 505.4 (M-H)⁻.

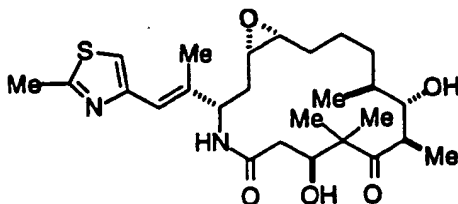
Exempl 4

Process for reduction of oxirane ring of epothilone and epothilone analogs.

- 5 To a two-necked flask was added chopped pieces of magnesium turnings (24 mg, 1.0 mmol). The flask was flame-dried under vacuum and cooled under argon. Bis(cyclopentadienyl)titanium dichloride (250 mg, 1.0 mmol) was added followed by anhydrous THF (5 mL). The stirring suspension was evacuated with low vacuum, and the reaction flask was refilled with
- 10 argon. The red suspension became dark, turning a homogeneous deep green after 1.5h with nearly all the magnesium metal being consumed. An aliquot (3.5 mL, 0.70 mmol, 3.5 eq) was removed and cooled to -78 °C under argon. To this solution was added epothilone A (99 mg, 0.20 mmol, 1.0 eq). The reaction mixture was warmed to room temperature and
- 15 stirred for 15 min. The volatiles were removed *in vacuo* and the residue was chromatographed two times on silica (25g), eluting with 35% EtOAc/hexanes to give 76 mg (80%) of epothilone C as a pale yellow viscous oil.

20

Example 5



- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

A. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-3,7-dihydroxy-12,13-epoxy-4,4,6,8,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-16(E)-heptadecenoic acid.

Tetrakis(triphenylphosphine)palladium(0) (1.17g, 1.01 mmol, 0.10 eq) was added to a solution of epothilone A (4.97g, 10.1 mmol, 1.0 eq) in degassed THF (100 ml) at room temperature and was stirred for 30 minutes under argon. Sodium azide (0.980g, 15.1 mmol, 1.5 eq) was added to the above reaction mixture followed by the addition of degassed water (10 ml). The reaction mixture was heated to 45 °C for one hour, cooled to room temperature, diluted with ethyl acetate (300 ml) and further diluted with water (150 ml). The aqueous layer was extracted with ethyl acetate (3x100 ml). The combined organic extracts were washed with brine (150 ml), dried (sodium sulfate), filtered and concentrated under vacuum. The oily residue was purified by flash silica gel chromatography (eluting 0-5% methanol/chloroform with 0.1% of acetic acid) to afford Compound A (1.84g, 34.0% yield) as glassy solid. MS (ESI⁺): 537 (M+H)⁺; MS (ESI⁻): 535 (M-H)⁻

B. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-3,7-dihydroxy-12,13-epoxy-4,4,6,8,16-pentamethyl-17-(2-methyl-4-thiazolyl)-5-oxo-16(E)-heptadecenoic acid.

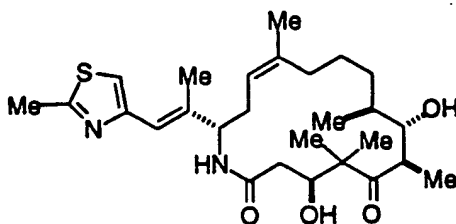
Platinum oxide (0.980g, 4.30 mmol, 1.25 eq) was added to a solution of Compound A (1.85g, 3.44 mmol, 1.0 eq) in absolute ethanol (137 ml). The reaction mixture was stirred vigorously under a hydrogen balloon for 16 hours at room temperature. The reaction mixture was filtered and the filtrate was concentrated under vacuum. The oily residue was purified by preparative HPLC (YMC S-15 ODS 50x500 mm column, 45 minutes/gradient, 0-100% B, 50 ml/min, retention time=17 minutes, A= 0.1% acetic acid /5% acetonitrile /95% water, B= 0.1% acetic acid /5% water /95% acetonitrile). The appropriate fractions were concentrated under vacuum and the residue was lyophilized from aqueous acetonitrile to afford Compound B (1.33g, 76.0% yield) as a colorless solid.

MS (ESI⁺): 511(M+H)⁺; MS (ESI⁻): 509 (M-H)⁻

C. [1S-[1R,3R (E),7R*,10S*,11R,12R,16S]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4-aza-
5 17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

Compound B (0.860g, 1.68mmol, 1.0 eq) was dissolved in anhydrous DMF (0.00250M, 672 ml) and degassed for one hour at room temperature. The solution was cooled to 0 °C, and anhydrous sodium bicarbonate (1.13g, 13.4 mmol, 4.0 eq) and diphenylphosphoryl azide
10 (1.85g, 6.72 mmol, 8.0 eq) were added under argon. The reaction mixture was kept at 4°C under argon and stirred 16 hours. The reaction mixture was then cooled to -60°C, and pH 7 phosphate buffer (400 ml) was added slowly to quench the reaction. Temperature was kept below -30 °C. The above mixture
15 was allowed to warm to room temperature slowly and extracted with ethyl acetate (1 liter). The aqueous layer was washed with ethyl acetate (4x300 ml). The organic extracts were combined, washed with 10% LiCl (500 ml), dried (sodium sulfate), filtered and concentrated under vacuum. The oily residue was purified by preparative HPLC (YMC S-15
20 ODS 50x500 mm column, 45 minutes/gradient, 0-100% B, 50 ml/min, retention time=35 minutes, A= 5% acetonitrile /95% water, B=5% water /95% acetonitrile). The appropriate fractions were concentrated under vacuum and the residue was lyophilized from aqueous acetonitrile to afford title compound (0.220g, 26.0% yield) as a colorless solid.
25 MS (ESI⁺): 493 (M+H)⁺; MS (ESI⁻): 491 (M-H)⁻

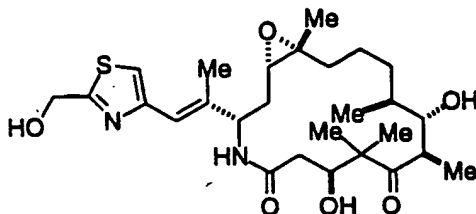
Example 6



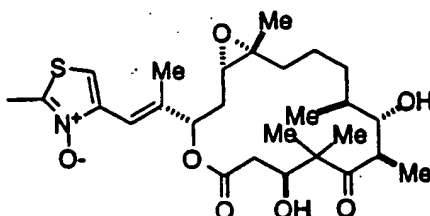
5 **[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione.**

Tungsten hexachloride (0.19 g, 0.49 mmol, 0.5 equiv) was dissolved in THF (5.0 ml) and the solution was cooled to -78°C. n-Butyllithium in
 10 hexane (1.6M, 0.63 ml, 1.0 mmol, 1.0 equiv) was added in one portion and the reaction mixture was allowed to warm to room temperature over 20 minutes (the solution turned dark green upon warming to rt). A 0.1M solution of the prepared tungsten reagent (0.79 ml, 0.079 mmol, 2.0 mmol) was added to Compound 4C (0.020 g, 0.039 mmol, 1.0 equiv) at
 15 room temperature. The reaction mixture was stirred a room temperature for 30 minutes and then was quenched with saturated NaHCO₃ (2.0 ml). The quenched solution was diluted with water (10 ml) and the solution was extracted with CH₂Cl₂ (4X20 ml). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated under
 20 vacuum. The inorganics were removed by passing the residue through a silica gel plug (eluting with 19/1 CHCl₃ / MeOH). The eluent was concentrated under vacuum. The residue was purified by phplc (YMC-S5 ODS, 30-100% B, A= 5% aq CH₃CN, B=95% aqueous CH₃CN, 3 ml/min., 220 nm., 30 min. gradient) and the appropriate fractions were
 25 concentrated under vacuum. The sticky solid was lyophilized from aqueous acetonitrile to afford title compound (4.3 mg, 29%) as a white solid. TLC: R_f = 0.57 (9/1 CHCl₃ / MeOH, visualization by UV); HRMS: (M+H)⁺ calc = 491.29436, found = 491.2934

Example 7

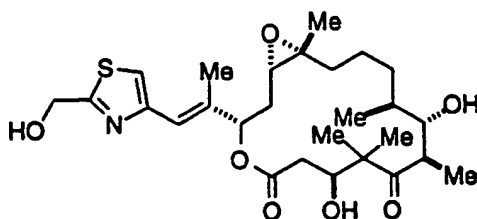


- 5 **[1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.**



- 10 **A. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione, N-oxide.**

- A solution of epothilone B (2.0 g, 3.9 mmol) in CH_2Cl_2 (30 mL) was treated with 3-chloroperoxybenzoic acid (1.0 g, 5.9 mmol) at 25 °C, under Ar for 2 h. An additional 0.5 g (3.0 mmol) of 3-chloroperoxybenzoic acid was added and the reaction mixture was then stirred for 2 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with saturated aqueous NaHCO_3 (75 mL), 5 % aqueous Na_2SO_3 (75 mL), H_2O (75 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2 , 4.5 x 30 cm, 2-10 % MeOH-CHCl_3 , gradient elution) to afford Compound A (1.04 g, 50 %) as a white solid. MS (ESI⁺): 524.3 (M+H)⁺; MS (ESI⁻): 522.5 (M-H)⁻.



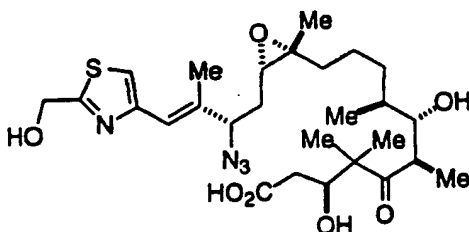
B. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione,

5 **[Epothilone F].** To a solution of compound A (0.46 g, 0.88 mmol) in CH_2Cl_2 (10 mL) in a resealable tube was added 2,6-lutidine (0.82 mL, 7.0 mmol) and trifluoroacetic anhydride (0.87 mL, 6.2 mmol) under Ar. The reaction vessel was sealed under Ar, heated to 75 °C (12 min), cooled to 25 °C, and the volatiles were removed under a steady stream of N_2 . The

10 reaction tube was then placed on a high vacuum pump for 15 min. The resulting residue was dissolved in MeOH (10 mL) and treated with ammonium hydroxide (28-30% NH_4 in H_2O , 1.0 mL). The mixture was heated to 45 °C (10 min), and the volatiles were removed *in vacuo*. The crude reaction mixture was purified by HPLC (YMC S-15 ODS 30 x 500

15 mm column, 50 % acetonitrile- H_2O isocratic conditions, flow rate = 20 mL/min, retention time = 28 min). The appropriate fractions were concentrated under vacuum and the residue was lyophilized from aqueous acetonitrile to afford Compound B (0.22 g, 48 %) as a white solid. MS (ESI⁺): 524.3 (M+H)⁺, 1047.6 (2M+H)⁺; MS (ESI⁻): 522.5 (M-H)⁻.

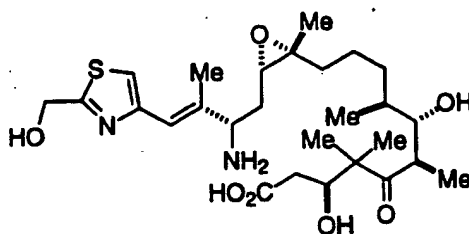
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C. (3S,6R,7S,8S,12R,13S,15S)-15-Azido-3,7-Dihydroxy-12,13-epoxy-4,4,6,8,12,16-hexamethyl-17-(2-hydroxymethyl-4-thiazolyl)-5-oxo-16(E)-heptadec noi acid. A solution of Compound B (0.18 g, 0.34 mmol) in

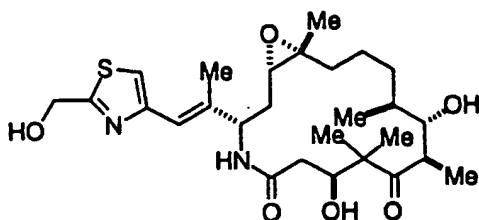
25 degassed THF (3.0 mL) was treated with a catalytic amount (40 mg, 3.4 x

10⁻² mmol) of tetrakis(triphenylphosphine) palladium(0) and the suspension was stirred at 25 °C, under Ar for 30 min. The resulting bright yellow, homogeneous solution was treated all at once with a solution of sodium azide (27 mg, 0.41 mmol) in degassed H₂O (1.5 mL).
 5 The reaction mixture was warmed to 45 °C for 1 h, diluted with H₂O (5 mL) and extracted with EtOAc (4 x 10 mL). The organic extracts were washed with saturated aqueous NaCl (15 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO₂, 2.5 x 15 cm, 95:5 CHCl₃-MeOH to 95:5.0:0.5
 10 CHCl₃-MeOH-AcOH gradient elution) to afford Compound C (39 mg, 20 %) as a colorless oil. MS (ESI⁺): 567.4 (M+H)⁺, 1133.6 (2M+H)⁺; MS (ESI⁻): 565.5 (M-H)⁻, 1131.8 (2M-H)⁻.



15 **D. (3S,6R,7S,8S,12R,13S,15S)-15-Amino-3,7-dihydroxy-12,13-epoxy-4,4,6,8,12,16-hexamethyl-17-(2-hydroxymethyl-4-thiazolyl)-5-oxo-16(E)-heptadecenoic acid.** To a 10 mL round-bottom flask charged with compound C (40 mg, 71 mmol) and PtO₂ (12 mg, 30 wt %) was added absolute EtOH (3 mL) under Ar. The resulting black mixture was
 20 stirred under one atmosphere of H₂ for 10 h. The system was then purged with N₂ and the reaction mixture was filtered through a nylon membrane (washing with 25 mL of MeOH). The solvents were removed *in vacuo* to afford Compound D (29 mg, 76 %) as a foam, which was sufficiently pure to use in the next step. LCMS: 541.3 (M+H)⁺.

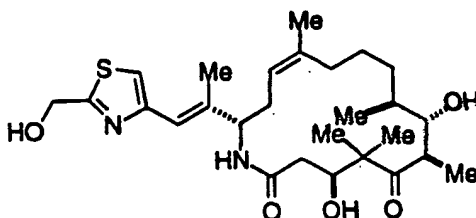
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E. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione.

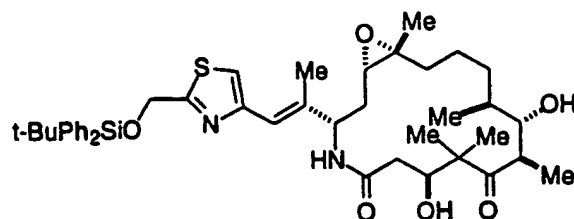
- 5 A solution of compound D (29 mg, 54 μ mol) in degassed DMF (21 mL) was treated with solid NaHCO_3 (36 mg, 0.43 mmol) and diphenylphosphoryl azide (46 mL, 0.21 mmol) at 0 °C under Ar. The resulting suspension was stirred at 4 °C for 19 h, cooled to -40 °C, diluted with 25 mL of pH 7 phosphate buffer (carefully adding such that the
- 10 internal temperature remains below -30 °C), and extracted with EtOAc (4 x 10 mL). The organic extracts were washed with cold 10 % aqueous LiCl (25 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified using a chromatotron (1 mm SiO_2 GF rotor, 2-5 % MeOH- CHCl_3 gradient elution) to afford the title Compound E (9.1 mg, 34 %) as
- 15 a colorless oil. MS (ESI^+): 523.2 ($\text{M}+\text{H}^+$); MS (ESI^-): 521.5 ($\text{M}-\text{H}^-$).

Example 8



20 **[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione.**

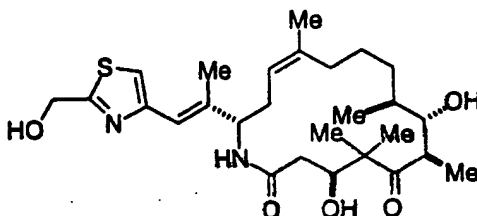
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A. [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-*tert*-butyldiphenylsilyloxymethyl-4-thiazolyl)ethenyl]-4-aza-17-

5 oxabicyclo[14.1.0] heptadecane-5,9-dione.

A solution of Compound 7E (6.8 mg, 13 mmol) in CH_2Cl_2 (0.5 mL) was treated with triethylamine (2.7 mL, 20 mmol), 4-*N,N*-dimethylaminopyridine (0.2 mg, 1.3 mmol) and *tert*-butyldiphenylsilyl chloride (3.7 mL, 14 mmol) at 0 °C under Ar. The reaction mixture was gradually warmed to 25 °C (1 h), cooled to 0 °C, quenched by the addition of saturated aqueous NaHCO_3 (1 mL), and extracted with EtOAc (4 x 2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2 , 1.0 x 5 cm, 2-5 % MeOH- CHCl_3 , gradient elution) to afford Compound A (7.0 mg, 71 %) as a colorless oil. MS (ESI⁺): 761.5 (M+H)⁺; MS (ESI⁻): 759.7 (M-H)⁻.



B. [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione.

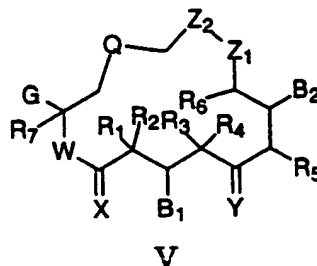
A solution of tungsten(IV) chloride (0.10 g, 0.25 mmol) in anhydrous THF at -78 °C was treated with *n*-BuLi (1.6 M in hexanes, 0.32 mL, 0.50 mmol) under Ar. The reaction mixture was warmed to 25 °C over 40 min and then recooled to 0 °C. An aliquot of the resulting deep-green,

homogeneous solution (0.2 mL, 20 mmol) was added to a 1 dram vial charged with compound A (7.0 mg, 9.2 mmol) at 0 °C under Ar. The reaction mixture was warmed to 25 °C, stirred for 30 min, quenched by the addition of saturated aqueous NaHCO₃ (0.5 mL) and extracted with EtOAc (4 x 1 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by preparative TLC (SiO₂, 20 x 20 x 0.025 cm, eluting with 5 % MeOH-CHCl₃) to afford an inseparable mixture of the silyl-protected (13Z) isomer of Compound B along with a small amount (<10%) of the minor (13E) isomer, which was immediately deprotected in the next step.

The silyl-protected isomeric mixture of compound B (2.3 mg, 3.1 mmol) was treated with 0.3 mL of a buffered solution of HF-pyridine in THF (2:1:0.5 THF/pyridine/HF-pyridine solution from Aldrich Chemical Co.) at 25 °C. After 1 h, the reaction mixture was neutralized with saturated aqueous NaHCO₃ (0.5 mL) and extracted with EtOAc (4 x 1 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (1 mL), dried (Na₂SO₄) and the volatiles were removed *in vacuo*. The residue was purified by preparative TLC (SiO₂, 20 x 10 x 0.025 cm, eluting with 5 % MeOH-CHCl₃) to afford title compound (13Z-isomer) along with an inseparable amount (<10 %) of the minor (13E) isomer (0.96 mg, 20 % for the two steps) as a thin film. MS (ESI⁺): 507.3 (M+H)⁺; MS (ESI⁻): 505.6 (M-H)⁻.

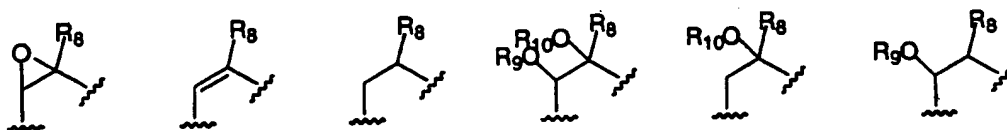
What is Claimed:

1. A compound of the formula



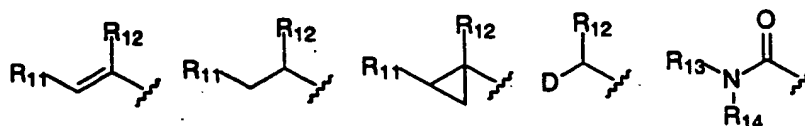
5

Q is selected from the group consisting of



10

G is selected from the group consisting of alkyl, substituted alkyl, substituted or unsubstituted aryl, heterocyclo,



15

W is O or NR₁₅;

X is O or H, H;

Y is selected from the group consisting of O; H, OR₁₆; OR₁₇, OR₁₇; NOR₁₈; H, NOR₁₉; H, NR₂₀R₂₁; H, H; or CHR₂₂; OR₁₇ OR₁₇ can be a cyclic ketal;

20

Z₁, and Z₂ are selected from the group consisting of CH₂, O, NR₂₃, S, or SO₂, wherein only one of Z₁ and Z₂ can be a heteroatom;

B₁ and B₂ are selected from the group consisting of OR₂₄, or OCOR₂₅, or O₂CNR₂₆R₂₇; when B₁ is H and Y is OH, H they can form a six-membered ring ketal or acetal;

D is selected from the group consisting of $\text{NR}_{28}\text{R}_{29}$, $\text{NR}_{30}\text{COR}_{31}$ or saturated heterocycle;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_{13} , R_{14} , R_{18} , R_{19} , R_{20} , R_{21} , R_{22} , R_{26} , and R_{27} are selected from the group H, alkyl, substituted alkyl, or aryl
5 and when R_1 and R_2 are alkyl can be joined to form a cycloalkyl; R_3 and R_4 are alkyl can be joined to form a cycloalkyl;

R_9 , R_{10} , R_{16} , R_{17} , R_{24} , R_{25} , and R_{31} are selected from the group H, alkyl, or substituted alkyl;

R_8 , R_{11} , R_{12} , R_{28} , R_{30} , R_{32} , R_{33} , and R_{30} are selected from the
10 group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, or heterocycle;

R_{15} , R_{23} and R_{29} are selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, cycloalkyl, heterocycle, $\text{R}_{32}\text{C}=\text{O}$, R_{33}SO_2 , hydroxy, O-alkyl or O-substituted alkyl, the
15 pharmaceutically acceptable salts thereof and any hydrates, solvates or geometric, optical and stereoisomers thereof, with the proviso that compounds wherein

W and X are both O; and

R_1 , R_2 , R_7 , are H; and

20 R_3 , R_4 , R_6 , are methyl; and

R_8 , is H or methyl; and

Z_1 , and Z_2 , are CH_2 ; and

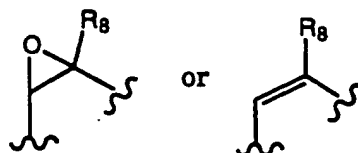
G is 1-methyl-2-(substituted-4-thiazolyl)ethenyl; and

Q is as defined above

25 are excluded.

2. The compound of claim 1 wherein

Q is



5 X is O;

Y is O;

Z₁, and Z₂, are CH₂; and

W is NR₁₅.

3. A compound selected from the group consisting of:

10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,13,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

[4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1,10-dioxa-13-cyclohexadecene-2,6-dione;

25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

30 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,14,17-trioxabicyclo[14.1.0]heptadecane-5,9-dione;

- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;
- 5 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1,11-dioxo-13-cyclohexadecene-2,6-dione;
- 10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-9-one;
- 20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-3,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13,16-hexamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,16-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-1-oxa-13-cyclohexadecene-2,6-dione;
- 35 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;

- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-6,8,8,10,12-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 15 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7, 9,13-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7, 9-tetramethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-4,8,8,10,12,16-hexamethyl-3-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-4-aza-17-oxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7, 9,13-hexamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl)ethenyl]-1-aza-13-cyclohexadecene-2,6-dione;
- 35 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-1,5,5,7, 9-pentamethyl-16-[1-methyl-2-(2-methyl- 4-thiazolyl) thenyl]-1-aza-13-cyclohexadecene-2,6-dione;

- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 5 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-13-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 10 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 15 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9-tetramethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-10-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 20 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 25 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-14-aza-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione;
- 30 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-11-aza-1-oxa-13-cyclohexadecene-2,6-dione;
- 35 [1S-[1R*,3R*,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12,16-pentamethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;

- [1S-[1R,3R,7R*,10S*,11R*,12R*,16S*]]-N-Phenyl-7,11-dihydroxy-8,8,10,12-tetramethyl-5,9-dioxo-4,17-dioxabicyclo[14.1.0]heptadecane-3-carboxamide;
- 5 [4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9,13-pentamethyl-2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide;
- [4S-[4R*,7S*,8R*,9R*,15R*]]-N-Phenyl-4,8-dihydroxy-5,5,7,9-tetramethyl-
- 10 2,6-dioxo-1-oxa-13-cyclohexadecene-16-carboxamide.
- [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.
- 15 [1S-[1R*,3R*(E),7R*,10S*,11R*,12R*,16S*]]-7,11-Dihydroxy-8,8,10,12-tetramethyl-3-[1-methyl-2-(2-methyl-4-thiazolyl)cyclopropyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione.
- 20 [4S-[4R*,7S*,8R*,9R*,15R*(E)]]-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[1-methyl-2-(2-hydroxymethyl-4-thiazolyl)ethenyl]-1-aza-13(Z)-cyclohexadecene-2,6-dione;
- and the pharmaceutically acceptable salts, solvates and hydrates
- 25 thereof.

4. A method of treating cancer in a patient which comprises providing an effective amount of a compound of claim 1 to said patient.
- 30 5. A method of treating hyperproliferative cellular disease in a patient which comprises providing an effective amount of a compound of claim 1 to said patient.

6. A method of providing an antiangiogenic effect in a patient in need of said treatment which comprises providing an effective amount of a compound of claim 1 to said patient.

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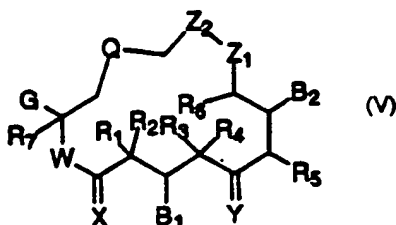
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(54) Title: EPOTHILONE DERIVATIVES

(57) Abstract: The present invention relates to compounds of formula (V).



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/12550

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : C07D 313/00 US CL : 549/346 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 549/346 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) REGISTRY, CAPLUS, MARPAT, MARPATPREVIEWS, APS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VICTORY, et al., Relative Stereochemistry and Solution conformation of the Novel Paclitaxel-like Antimitotic Agent Epothilone A. Bioorg. Med. Chem. Letts., 1996, Vol. 6, No. 7, 893-898, see entire document.	1-61-6
X	WINKLER et al., A Model for the Taxol (Paclitaxel)/Epothilone Pharmacophore. Bioorg. Med. Chem. Letts., 1996, Vol. 6, No. 24, 2963-2966, see entire document.	1-61-6
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categorization of cited documents:	T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer <i>Laura Lutz</i> LAURA LUTZ Telephone No. (703) 308-1235